

RECENT DEVELOPMENTS IN ALCOHOLISM

VOLUME 16
RESEARCH ON
ALCOHOLISM TREATMENT

EDITED BY MARC GALANTER

An Official Publication of the American Society of Addiction Medicine
and the Research Society on Alcoholism.
This series was founded by the National Council on Alcoholism.

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ALCOHOLISM

VOLUME 16
RESEARCH ON
ALCOHOLISM
TREATMENT

Methodology
Psychosocial Treatment
Selected Treatment Topics
Research Priorities

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JOHN P. ALLEN, RICHARD FULLER,
RAYE LITTEN, MICHAEL ECKARDT,
MARY MCAUL, and PETER MONTI

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Preface

From the President of the Research Society on Alcoholism

The sixteenth volume of Recent Developments in Alcoholism contains the latest information on the field of alcoholism treatment research. This scholarly volume includes comprehensive reviews of the methodologies available to evaluate treatment outcome, state-of-the art psychosocial interventions, and recent advances in pharmacological adjuncts to treatment that are currently available and those on the brink of application. Other sections of the book address special issues in the treatment of alcohol dependence, including the treatment of the adolescents and other unique populations, the management of tobacco dependence, and the role of spirituality in recovery, among others. The clinician will find these reviews an important resource for learning about evidence based treatments for alcoholism, and the researcher will find the synthesis of recent developments informative and forward looking. The research agenda for the future rests soundly on the progress to date and additional advances in the treatment of alcoholism can be predicted in the near future.

Stephanie O'Malley, Ph.D.
President, Research Society on Alcoholism

Preface

From the President of the American Society of Addiction Medicine

This excellent volume presents investigations covering a wide spectrum of scientific issues. It is also evident that many of these articles have clinical significance, ranging from assessments of disorder, monitoring clinical progress, and behavioral and pharmacological interventions. Indeed, society, in general, and persons suffering from the complications of alcohol consumption, in particular, benefits most by an inextricable collaboration between clinicians and scientists. Scientific endeavors are more greatly appreciated when their application to clinical care is understood and clinical care is more likely to be effective when it is founded in fundamental scientific principles.

Recognizing the fundamental need for a close relationship between science and clinical care, clinicians also face many challenges to integrating technological advances derived from important scientific studies. These challenges include the lack of adequate understanding among payers (managed care organizations and other private and public insurers) and the under-representation of alcohol and substance abuse issues among the priorities of medical schools, residency training programs and state licensing boards. While these are challenges, they also present opportunities for clinicians and investigators such as the authors of this volume to continue collaborations to bring these findings from the "bench to the trench."

Lawrence S. Brown, Jr., MD, MPH
President, American Society of Addiction Medicine

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I

Introduction

Enoch Gordis, Section Editor

Research on Alcoholism Treatment

Enoch Gordis

Thirty years ago when I first began treating alcoholism, writing an introduction to a book on alcoholism treatment research would have been a challenge. At that time, alcoholism treatment was in its infancy, and alcoholism treatment research was nearly nonexistent. The challenge, therefore, would have been finding enough to say. Writing this introduction to *Recent Developments in Alcoholism, Volume XVI, Research on Alcoholism Treatment* has also been a challenge—not because there is so little to say about developments in alcoholism treatment research, but because there is so much.

As can be seen from the many subjects addressed in this volume, alcoholism treatment—from behavioral therapies to new medications—and the science that drives it, has come far. We know more about alcoholism treatment, and we have also learned much about how to do treatment research. This is important. Because alcohol treatment developed apart from the mainstream of medical science, the standards for controlled clinical trials—randomization, blind design, placebo—that we would insist on for cancer, heart disease, diabetes, or other major illnesses—were not applied to early alcoholism treatment. All too often, treatments were tried because they sounded as though they might work, rather than because of any definitive evaluation of their efficacy. I am happy to report that this situation has changed. One important reason for the change is the development and refinement of methods for alcoholism research. In 1986, the first large-scale clinical trial in alcohol research on disulfiram demonstrated two important things. First, it demonstrated that clinical research standards could be applied to alcoholism treatment. Second, and in my opinion more importantly, this trial defined critical methodology, such as methods to measure compliance. Since that time, alcohol researchers have continued to develop and refine the definition of treatment efficacy and how it is measured.

The authors of the chapter on "Methodology" explore some of the important developments in this area, including how science is searching for biomarkers that would give researchers and clinicians alike an objective means of diagnosing alcoholism and monitoring the effectiveness of treatment protocols.

New and refined methods of conducting alcoholism clinical research have led to significant growth in research aimed at evaluating existing behavioral therapies. Research progress in recent years has led to a number of important findings about traditional behavioral therapies and to clinically applicable findings about newer behavioral therapies. One study in particular, Project MATCH, supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), has provided valuable insights that are guiding current clinical research on a number of different fronts. The primary finding that matching patients to specific treatments on the basis of their characteristics did not significantly affect treatment outcome was a major rebuttal of what had been accepted clinical wisdom for many years. However, more importantly, the work done by the Project MATCH investigators to prepare for the trial, including developing diagnostic instruments, criteria for the delivery of three different types of behavioral therapies, and detailed training manuals for conducting therapies provided clinicians with better tools and has also stimulated research into refining each of the therapies evaluated. Developments in these therapies, including Cognitive Behavioral Therapy, Motivational Enhancement Therapy, and Twelve-Step Facilitation are each addressed in the chapter on Psychosocial Treatment.

Alcohol research has not been limited to evaluating existing therapies. New approaches to treating alcohol problems have also been developed by alcohol research. One of these is brief intervention which has been found effective in treating alcohol problems in primary care practices. Because human beings are notoriously complex organisms, there are likely to be any number of influences that are important to a successful treatment outcome. Alcohol researchers have begun to define some of these and for whom they are important as indicators of treatment success—or failure. These include the known link between alcohol use and smoking. It appears, for example, that contrary to popular wisdom, treating nicotine dependence along with alcohol dependence does not negatively affect treatment outcome. Another area of growing focus is treating adolescents with alcohol problems. Like adults, adolescent drinkers are a heterogeneous group. There is growing concern about the use of alcohol by adolescents particularly in the light of epidemiological evidence that the younger an individual begins to drink, the higher the risk for developing an alcohol problem later in life, and evidence of cognitive deficits in adolescents who are heavy drinkers. These special factors in alcohol treatment are among those discussed in the concluding chapter on "Selected Treatment Topics."

Although psychological therapies can help many alcohol-dependent persons reduce their drinking and maintain abstinence, these approaches alone are not effective for many patients. Thus, developing effective pharmacotherapies for alcoholism treatment has become a top priority of alcohol research.

Research is underway to determine how alcoholism treatment medications work, the potential therapeutic value of using pharmacotherapy for a longer period of time, and which subsets of patients are most likely to benefit from new pharmacological treatments. Here, we have begun to see what I believe is the future of alcohol research where findings from neuroscience research (and at some point, genetics research) form the basis of new classes of medications specifically designed to target biological mechanisms that result in destructive behaviors. Although we are far from having the proverbial "silver bullet" for treating alcoholism (and, given the complexity of the disease, it is doubtful that we will ever find one medication to treat all forms of alcohol dependence), we have already begun to see the fruits of neuroscience research translated into medications available as adjuncts to behavioral therapy for treating alcoholism.

Key among these medications has been naltrexone. A product of neuroscience research, naltrexone, an opiate antagonist, is the first medication approved to help maintain sobriety after detoxification from alcohol since disulfiram was approved in 1949. The European drug acamprosate is awaiting approval by the FDA. Both medications, it has been found, reduce craving in alcoholics with varying degrees of success. What is exciting, however, is that each medication appears to work on a different brain mechanism underlying the craving that most clinicians believe is a critical factor in patient relapse. It is exciting because it shows that we can alter alcohol's effects in the brain at the biological level. This finding has increased the intensity of research efforts aimed at unraveling the complex of neural pathways that are involved in alcohol dependence and developing medications that will ultimately improve treatment outcome.

Combining behavioral therapies with pharmacotherapies is likely to be the next important advance in alcoholism treatment. There are several ways in which behavioral and pharmacological therapies could work together. One way is that one therapy might continue to function if the other fails. This resembles treatments using two antibiotics where one medication can serve as a backup if resistance to another develops. A second way is that each therapy might increase the efficacy of the other. For example, verbal therapy may enhance compliance with pharmacological therapy which in turn reduces craving, allowing the patient's more complete attention to the verbal therapy. Project COMBINE, a new large-scale randomized study supported by the NIAAA, will take advantage of the knowledge learned from Project MATCH to further explore the coupling of verbal and pharmacological therapies. In Project COMBINE, mixed pharmacological and behavioral approaches will be evaluated to determine what combinations work best in the treatment of alcohol dependence. Research on naltrexone, acamprosate, and other medications, as discussed in the chapter on "Pharmacotherapy", are just the tip of the iceberg. As we gain greater understanding of the biology of addiction and of the links between biology and behavior, I have no doubt that the arsenal of medications available to treat alcohol problems in conjunction with behavioral therapies will expand substantially.

Alcoholism clinicians have access today to a wide range of treatment options for their patients. Some of these treatments have been around for a long time. Others are relatively new. Continued research on alcohol's effects in the brain and on the links between brain and behavior is likely to provide clinicians with a range of highly specific medications that will change the fundamental nature of addiction treatment. Thirty years ago our best clinical practice helped some but far from all of our alcoholic patients. Today, our best science is upping the odds that those whom we treat will recover.

Methodology

John P. Allen, Section Editor

Overview

John P. Allen

Although quite diverse in content, each of the five chapters in this section of Recent Developments bears on significant methodological issues in alcohol treatment research. The various papers address complex statistical and design topics and recommend important new variables that should be considered in future outcome research.

Explicitly and implicitly, each of the chapters alludes to Project MATCH, the largest trial ever conducted on behavioral treatments for alcohol problems or, for that matter, for any psychiatric problem. Among the major methodological advances of Project MATCH were employment of hierarchical linear modeling, rather than less sensitive repeated measures of statistical techniques, to evaluate the longitudinal effects of treatment; use of adaptive "urn" randomization to equate experimental groups on key patient baseline characteristics; application of biochemical markers to corroborate self-reported outcome drinking status; incorporation of a specific and detailed battery to assess counselor and counselor-client interaction characteristics; quantitative and multifaceted evaluation of in-treatment and extratreatment process variables; and development and inclusion of several new client measures that have since been widely adopted by the field. All of these important methodological features are elaborated and expanded on in the current collection of papers.

It is not possible to fully address all of the issues raised by this rich set of papers in a brief space. Nevertheless, a brief synopsis of each of the papers can be offered.

Bob Stout's paper, while acknowledging important statistical and methodological advances in evaluating alcohol treatment, addresses several inadequacies that yet remain in this endeavor, offers insightful recommendations, and urges new lines of research on technical issues that continue to require resolution before more promising methodologies can be employed in the field.

He addresses fundamental design issues surrounding issues such as equating experimental groups, reducing bias in "effectiveness" (naturalistic treatment setting) research, more precisely estimating power, more fully operationalizing treatment process variables, more sensitively exploring site characteristics mediating or moderating overall treatment effects, formulating integrated outcome measures, and conducting longitudinal analyses of treatment effects. He concludes the chapter by summarizing several new statistical approaches that may be wisely incorporated into future research projects in the field.

The assessment chapter offers a perspective on several recent significant achievements in measures to screen and diagnose patients as well as to develop treatment plans individualized according to relevant characteristics of patients. The chapter also suggests a host of issues that merit future research attention. Both investigation of and appropriate management of medical problems rely on accurate, comprehensive assessment, and the alcohol field is fortunate in the wealth of useful measures now available on the many complex aspects of the problem.

Lisa Najavits' chapter strongly argues that far more research should focus on clinicians delivering alcohol treatment since most substance abuse disorder treatment involves a large component of counseling or psychotherapy. She reviews major findings on characteristics of counselors most successful in retaining clients in treatment and in effecting behavioral change. Although studies on the topic have rather uniformly found that counselors differ widely in their rates of drop out and improvement, the reasons for this remain largely unexplored. Some characteristics, however, recurrently emerge from studies on the topic. Notably, adherence to the assigned treatment protocol appears to be associated with improved outcome. Similarly, to the extent that treatments are more precisely defined by procedural manuals, counselors differ less from each other in retention and improvement rates. Counselor empathy has also generally been found associated with positive effects. She concludes her chapter by offering a series of suggestions on future studies of alcohol counselor effects.

The chapter on the use of biomarkers as aids in identifying relapse reviews studies beginning in the 1980s that considered the relationships of serum-based lab tests to recurrence of drinking by patients in alcohol treatment or aftercare. Most of these studies have included carbohydrate deficient transferrin (CDT). Although findings differ somewhat, all but one of the projects showed that relapse to drinking is associated with reelevation in values of several lab tests. In two of the investigations, the researchers found that CDT reelevation often preceded the patient's verbal acknowledgement of return to drinking. Although self-report measures tend to be more sensitive than biochemical measures, use of the two sources of information in combination is recommended.

Finally, Jalie Tucker's chapter highlights findings on resolution of alcohol problems outside of the formal treatment system. She notes that the topic is of considerable interest in its own right because many individuals with alcohol problems resolve them in this manner, and also that findings surrounding the natural recovery process may have important implications for reducing

barriers to entering formal treatment, as well as for developing new formal interventions. Particularly interesting, she concludes that negative events associated with drinking generally prompt attempts at moderation or abstention but that to be ultimately successful, these attempts must be reinforced by subsequent positive experiences. Many of those who resolve alcohol problems on their own feel standard alcohol treatment approaches are in some way inappropriate for them, an important consideration, it would appear, in facilitating access to formal treatment. Following her summary of findings on the topic, she offers a useful blueprint for future needed research.

In short, the chapters of this section are important in that they rather clearly summarize what we currently know about these major topics in the field, but perhaps even more, because they suggest directions that future studies might wisely take.

Assessment of Alcoholic Patients

Advances and Future Challenges

John P. Allen

Abstract. Noteworthy advances have been made in methods of assessing patients suffering alcohol problems. More than one hundred measures are now available to assist clinicians and researchers in screening for such problems, diagnosing them, and developing treatment plans individualized according to relevant patient characteristics. This chapter reviews progress in assessment supporting each of these activities and suggests directions for future research. It concludes by identifying a series of research issues that cut across multiple domains of alcohol assessment.

1. Introduction

The National Institute on Alcohol Abuse and Alcoholism in conjunction with experts in the field of assessment of substance abuse has just revised *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*.¹ This popular handbook is a compendium of approximately 100 useful, valid measures. Equally important, the volume includes state-of-the-art reviews of various assessment domains that influence clinical management of patients from initial screening to evaluation of treatment outcome. Consideration of these review chapters allows one to form impressions of some of the major achievements in the domains of assessment and to identify several of the challenges that future research and test development efforts can resolve. These are addressed in this chapter according to three stages of patient care: screening, diagnosis, and treatment planning. The chapter concludes with a brief section dealing with broad research questions that bear on multiple assessment domains.

2. Self-Report Screening Measures

Self-report scales are the most common means of screening for alcohol problems. These instruments typically ask patients directly about their drinking behavior, its adverse consequences, and symptomatic features of alcohol dependence. Such tests tend to be quite brief and can be administered orally, in written form, or via computer.

Recent advances in the field include evaluation of alcohol screening scales that are embedded in more global content health risk appraisal surveys, as opposed to the more typical way of administering them as stand-alone measures; construction of measures more sensitive to specific groups such as adolescents, older adults, and pregnant women; and formulation of clinical recommendations for using test results as the basis of feedback to help motivate behavioral change. Newer measures often include items dealing with tolerance, very recent consumption, and at-risk drinking symptoms, all of which seem to enhance the validity and utility of these scales. Although research reports on the topic usually provide statistics on the sensitivity and specificity of scales, it has become increasingly common also to offer positive and negative predictive values, information that may be even more informative to clinicians in evaluating the appropriateness of a screening test for the particular populations they serve.

A variety of future research challenges exist. Perhaps most importantly, is the establishment of a "gold standard" criterion for evaluating the predictive accuracy of screening tests. To date, self-report measures have generally been judged on the basis of their ability to predict a diagnosis of alcohol abuse or dependence that would be given on the basis of an interview that is more extensive than the screening test. Nevertheless, to the extent that the screening test and the diagnostic interview often include many of the same items, they would be expected to correlate rather highly on that basis alone. Further, both screening measures and the diagnostic measures assume the accuracy of self-report information. (Although some "covert content" measures, such as the MacAndrew Alcoholism Scale exist,² they are not as widely used as in the past.) The ideal "gold standard" against which a self-report screening instrument should be evaluated would itself be perfectly valid and not rely on self-report responses. Development of objective measures of alcohol dependency, at-risk drinking, etc. will require much effort.

The plethora of excellent self-report screening measures already available argues against the need for constructing new scales. Rather, more intense psychometric research should focus on especially promising existing instruments. To date, many of these have been studied in only a small number of projects.

There is a growing tendency to develop screening measures specific to various types of patients. Clearly, some of these efforts have been quite successful.^{3,4} Nevertheless, a more parsimonious strategy might involve maintaining the same item set but simply changing the cutoff score, as needed, for screening particular types of patients, an approach exemplified in recent studies of the Alcohol Use Disorders Identification Test with women and adolescents.⁵

Research is needed to determine if this approach is adequate for other screening tests as well or if screening measures with different item content are required for various target populations.

Inasmuch as the validity of self-report screens is a function of patient variables, particularly, willingness to self-disclose and accurate memory, studies to develop strategies to maximize the validity of screening measures and the conductiveness of the interview setting to elicit full honesty and cooperation are also needed.

It is commonly assumed that feedback to patients based on their responses to screening items, such as showing the patient how his or her drinking quantity and frequency compare with those of age- and gender-based peer groups, is a potent stimulus for change. Unfortunately, there has been little research specifically on this issue or on strategies for feedback that would prove most motivating. Such studies would be helpful.

Most research on alcohol screening is restricted to its application in primary health care. Alcohol screening would also be useful in other contexts such as employment selection, legal matters, and managerial oversight of employees responsible for health or safety. There has been little examination of the validity of self-report screening tests in these contexts, some of which appear less facilitative of candid self-report.

Perhaps of greatest concern, despite the wealth of existing good instruments, screening for alcohol problems has not yet become standard practice in health care settings.⁶ Investigations of the barriers to their underutilization as well as techniques to overcome these impediments would thus have considerable applied value.

3. Biochemical Markers

The recent approval by the Food and Drug Administration of carbohydrate deficient transferrin (CDT) as an indicator of heavy drinking hallmarks the success of efforts to discover useful alcohol biomarkers. CDT is the first marker to be so approved, although a variety of other markers of heavy drinking, most of which reflect organ damage often associated with chronic alcohol consumption, have long been available to clinicians.

Biological tests may contribute to assessment of alcoholic patients particularly by aiding in initial recognition of these problems and in early recognition of relapse to drinking by patients in treatment. As with self-report screening measures, they may also serve as a basis for feedback to patients to augment motivation to change, as well as to elucidate differential diagnosis by determining the possible contribution of heavy drinking to medical or behavioral disorders. Because considerably less research has been done on these capabilities, the discussion here is limited to biomarkers for screening and relapse recognition.

In the past few years, there have been three advances in the domain of biomarkers of heavy drinking. Markers (e.g., gamma glutamyltransferase,

macrocytic volume, and CDT) are being increasingly employed in various combinations to permit more accurate screening of alcohol problems than use of them separately. Interestingly, combining markers in pairs or triads generally raises sensitivity without substantially reducing specificity since, at least to some extent, alternative markers accurately identify somewhat different types of heavy drinkers.⁷

Second, several new markers have recently been discovered, such as 5-hydroxytryptophol, beta hexosaminadase, and acetaldehyde adducts. Initial findings on the potential values of these new markers are quite encouraging. Work is also continuing on development of a miniaturized transdermal alcohol sensor, a device that offers a continuous measure of alcohol consumption by reflecting ethanol extruded in sweat. Although this device cannot be used for routine screening, it could be employed by clinicians to evaluate changes in drinking during or after treatment and could also provide outcome information in clinical trials of alcohol interventions.

The third advance in the domain of biomarkers has been their application as aids in early identification of relapse to drinking. CDT does particularly well in this respect and, in fact, may indicate relapse well in advance of the patient acknowledging a return to drinking.⁸

Although more than 1200 studies of alcohol biomarkers have been published, additional research on the topic is still needed. Most importantly, investigations are needed to clarify how alternative markers respond to drinking. These would include derivation of dose-response and decay curves, as well as analyses of the way various drinking patterns influence different markers. The latter analyses would provide answers to fundamental questions dealing with the intensity, pattern, and duration of drinking needed to influence the marker. Answers to these questions might well differ if the marker were being considered for screening versus relapse detection.

Further developmental research is also needed on the new markers that have been proposed. In particular, some of these markers may assist in screening adolescents, women, older adults, and binge drinkers. Generally, with the currently available markers, a fairly sustained period of heavy drinking is needed to prompt elevation. Conversely, many of the newer markers reflect any recent drinking but do not necessarily demonstrate heavy drinking per se.¹⁰

Similarly, research is needed to identify how varying subtypes of drinkers respond to alternative markers. It appears, for example, that some patients may be best identified by CDT, GGT, or MCV.⁹

Another continuing research need is derivation of algorithms to optimally combine results across tests. Several strategies have been proposed for integrating lab test results. These include the use of ratios of markers; sequencing markers, simultaneous use of two or more markers, where results are labeled as positive if any of the component test results is above the cutoff value; the use of weighted sums of marker scores based on formulas derived from sophisticated statistical techniques such as discriminant function; and so on.¹¹ Similar variations exist for scoring relapse markers, that is, comparison with a predetermined

cutoff value (usually the test's screening cutoff value) or "ipsatively" in which the patient's own current score is contrasted with the lowest value observed to date.⁸ Research is needed to optimize the use of tests in combination, as well as to determine the optimal way of scoring them.

Finally, studies would be helpful on possible issues of reactivity (i.e., does the awareness of patients that their verbal report of drinking is subject to biochemical corroboration influence the veracity of self reports of drinking status?).

4. Self-Report Measures of Consumption

There are several reasons for measuring alcohol consumption precisely:

1. The physical risks associated with alcohol use are somewhat related to current and previous levels of consumption.¹²
2. Alcohol treatment efficacy trials typically consider posttreatment consumption as the primary outcome variable, and alternative interventions may influence drinking behavior in different ways (e.g., naltrexone may have a particular impact on delaying the onset of relapse and truncating its duration).
3. Certain interventions, especially those motivationally focused, rely heavily on the positive impact of giving patients detailed feedback on their drinking behavior.
4. Relapse prevention therapies are often based on precise understanding of the topography of posttreatment drinking.

A broad range of self-report alcohol consumption measures is available. One group involves techniques that ask patients to summate their drinking behavior across a fairly long period of time (quantity–frequency approaches). A second category asks patients to enumerate, as precisely as possible, their drinking occasions and the number of drinks consumed during each. The recall period may be the very recent past or may be quite distant. Memory cue-based strategies in which the patient is presented with a calendar on which key event dates are indicated might assist in recalling drinking on a day-to-day basis. This approach is termed the "time-line follow-back."¹³ Alternatively, patients may be asked to maintain a daily diary for documenting in real time their drinking behaviors and often the stimuli and consequences of the episodes.

Although much has been achieved in the development of consumption measures, as with biomarkers, additional research is needed to determine the extent to which reporting or recording one's drinking is reactive. The degree of reactivity might be a function of drinking behavior, the frequency with which the measure is taken, and the amount of experience that the patient has had with recording. Although reactivity might offer therapeutic benefits, if the measure is used as an index of treatment outcome, the measure and the intervention would be confounded. As for self-report screening, additional research

is needed on strategies to maximize the accuracy of self-report measures and identify potential sources of invalidity.

Data collected by accurate drinking measures are of extreme value in treating particular patients and also in enhancing our understanding of general drinking patterns and relapse to drinking. A key research question in this regard concerns the pattern of return to drinking that constitutes a "clinically significant relapse," one that is highly likely to lead to adverse consequences.

Several of the drinking consumption measures are quite labor- and time-intensive for the clinician, the researcher, and the patient, and, hence, development of user-friendly computerized versions of consumption measures is also strongly recommended.

5. Diagnostic Measures

The chapter in the Assessment Handbook by Maisto and McKay¹⁴ reviews diagnostic instruments under four headings: nomenclature or assignment of a diagnosis, determination of severity of dependence, measurement of preoccupation with controlling one's alcohol use, and specification/quantification of adverse consequences of drinking. The primary goal of diagnostic instruments is to facilitate discussion among clinicians by using terms, especially "alcohol dependence" and "alcohol abuse," clearly, consistently, and parsimoniously. Formal diagnosis according to consensually defined criteria also advances research on treatment efficacy by specifying the types of drinkers included in a trial. Finally, formal diagnosis assists in satisfying requirements for third party reimbursement of alcohol services.

Beyond describing phenomena related to alcohol use or withdrawal, secondarily, diagnostic scales may also suggest fundamental features of treatment including intensity, setting, goal as abstinence or moderation, and medicational management of withdrawal. (The Clinical Institute of Withdrawal assessment (CIWA),¹⁵ for example, has proven useful as a basis for determining the need for benzodiazepines for withdrawal management.) Another secondary application of several of the diagnostic measures is as a foundation for patient feedback to motivate behavioral change. For example, the motivational enhancement intervention evaluated in Project MATCH¹⁶ included discussing scores on the Drinker Inventory of Consequences (DrInC)¹⁷ with patients.

Nomenclature measures differ in their degree of structure. Fully structured ones employ a standardized interview or paper-and-pencil questioning format requiring simple "yes" or "no" responses to items dealing with cardinal features of alcohol dependence. Unstructured diagnostic measures, on the other hand, allow the interviewer considerable flexibility in asking the patient to describe and elaborate on symptoms. For research purposes, structured measures are likely to be preferred since they have high and readily computable reliabilities. On the other hand, clinicians may prefer the richness of detail of the patient's experience of symptoms revealed by responses to unstructured measures.

Among the advances made in diagnostic measures, particular attention should be given to DrInC.¹⁷ The strengths of this measure include a large number of items designed to tap several alcohol consequence dimensions, a normative database that is both contemporary and consists of a large number of patients from geographically dispersed treatment sites and inclusion of questions designed to capture the adverse effects of drinking that might be experienced, particularly by women. Also valuable is the comprehensive manual on the test available from the National Institute on Alcohol Abuse and Alcoholism. DrInC is rapidly becoming the standard measure of adverse consequences of alcohol use in research in the field.

There are many directions that future research related to alcohol diagnostic measures might pursue.

Although the conceptual basis of the diagnostic nomenclature for alcohol problems is profound, it is important to bear in mind that it emphasizes dependence per se, rather than drinking patterns and quantities. Collateral diagnostic systems might also focus on drinking behavior and its adverse consequences. Diagnostic systems and instruments to measure drinking behavior is also likely to satisfy the needs for communication among clinicians, determination of inclusion/exclusion of subjects in clinical trials, and reimbursement for alcohol services. Further, such systems might stimulate more compelling discussion with the public, policy makers, and third party reimbursers about the effects of alcohol problems on society and the attention that they warrant.

As noted earlier, development of the CIWA and the DrInC represent significant contributions to the diagnosis of alcohol problems. Several new withdrawal agents are currently under development, and construction of CIWA-like instruments might assist clinicians in choosing among them and in determining optimal dosing schedules. Beyond this, research on the possible relationships of "kindling" to findings on the CIWA and similar future scales would be quite informative. Future research on the DrInC might focus on determining its relevance to possibly unique patterns of adverse consequences suffered by alcoholics as a function of their demographic characteristics of age, gender, ethnicity, and psychiatric status.

6. Treatment Planning Instruments

Treatment planning instruments are designed to assess patient characteristics that should influence the nature, intensity, and setting for treatment, so that it can be most helpful to a patient. The domain of such instruments is multi-faceted and Donovan's chapter¹⁸ in the Assessment Handbook reviews them under these headings:

- readiness to change
- expectations of particular alcohol effects
- self-efficacy expectancies

- drinking-related locus of control
- family history of alcoholism
- extratreatment support for abstinence

Further, he notes that treatment planning involves the

integration of assessment information concerning the person's drinking behavior, alcohol-related problems, and other areas of psychological and social functioning to assist the client and clinician develop and prioritize short- and long-term goals for treatment, select the most appropriate interventions to address the identified problems, determine and address perceived barriers to treatment engagement and compliance, and monitor progress toward the specified goals, improved psychosocial functioning, and harm-reduction.

Studies have indicated that, with successful alcohol treatment, the sense of self-efficacy, awareness of personal control over drinking, and the readiness to change one's drinking behavior tend to increase. Similarly, beliefs about the benefits of drinking diminish. These positive effects are reflected in changes in scores on various treatment planning instruments.

There have been major advances in this domain of assessment in recent years. These include both methodological advances in measurement approaches, as well as expanded coverage of potentially relevant information for treatment planning. Although, traditionally and most commonly, scales to evaluate this class of variables are fully structured fixed-response inventories, recently, a few scales have been constructed that employ a semi-structured interview format designed to elicit open-ended responses. Guidelines are provided for subsequent scoring or categorization of responses. Examples of these include the Individualized Self-Efficacy Survey¹⁹ and the Substance Abuse Relapse Assessment.²⁰ New content areas include measures of negative expectancies about alcohol's effects, measures of support for drinking and abstinence from the patient's social environment, and measures to directly inform clinicians on patient treatment placement. Although positive beliefs about alcohol's effects may prompt initial use of alcohol, it is, perhaps, more the growing awareness of the adverse effects of drinking that motivates entry into treatment and, hence, measures of negative alcohol expectancy appear useful. So, too, research suggests that key individuals in the patient's work or family environment may powerfully reinforce efforts to drink or to abstain. Finally, stringent controls on the use of treatment resources, as well as clinical accountability, argue the need for objective criteria to assign patients to treatments that are most clinically effective and cost-effective. Granted the importance as well as the scope of this domain of assessment, considerable research remains to be done.

The large number of treatment planning scales is probably bewildering to most practicing clinicians. Although clinicians should select measures on the basis of the philosophy of the treatment program as well as the treatment options available, consideration must also be given to the psychometric characteristics of alternative measures. Unlike the area of self-report and biochemical

screening measures, where a number of "horse race" studies have been conducted that directly contrast validities of competing instruments,²¹ there are, as yet, few comparative studies within the various dimensions subsumed under treatment planning.

Second, most of the scales in this domain have been validated in terms of their relationships to pretreatment or posttreatment drinking characteristics. Granted that this information is useful in establishing the relevance of the domain, the most critical concern is the implication of scores for selecting alternative treatments or settings. Adequately evaluating these measures requires controlled clinical trials that are costly by their very nature. There are as yet few such studies. Preliminary findings suggest that controlled research would be warranted to determine, for example, if efforts targeted at reducing particularly salient positive expectancies about drinking improve outcomes. Also, in the light of the influence of the patient placement criteria of the American Society of Addiction Medicine,²² more research is warranted to establish their validity in terms of cost savings and clinical efficacy.

Patient taxonomies have been developed and, in a few instances, cross-validated using measures of readiness, alcohol expectancies, self-efficacy, and the Alcohol Use Inventory.²³ Creation of these subtyping systems has employed cluster analysis, profile analysis, or logical considerations.²⁴ As with individual scales on treatment planning instruments, the relevance of these classificatory systems should be established by demonstrating that incorporating them into clinical practice enhances outcomes.

A major area of research suggested by Donovan is the value of using treatment-planning instruments in combination. This topic, as well as studies on strategies to encourage counselors to appropriately incorporate this rich array of instruments into their clinical practice, are urged.

7. Cross-Cutting Issues

Beyond the needs for research in particular assessment domains, several applied and conceptual issues related to assessment in general merit further research attention. The large number of measures, especially related to self-report screening and exploration of alcohol effect expectancy, suggests that, for at least some variables relevant to patient care, what is most needed now is more intense research on existing, promising scales, rather than construction of new measures. Beyond the sheer number of competing measures, the paucity of studies on many of them makes it exceedingly difficult for clinicians and researchers to determine which measures would best satisfy their needs. Obviously, as more is learned about the phenomenon of alcohol dependence and the recovery process, the development of measures for new dimensions may be necessary in the future. In the interim, however, research might particularly concentrate on the development of more comprehensive norms for measures; refinement/development of abbreviated scales for lengthy, but helpful,

scales; and determination of the way measures relate to each other and specifically to the treatment process. Most importantly, it would be useful to determine how the information provided by various measures contributes to the effective assignment of patients to treatment options that differ in intensity and modality.

Studies evaluating the effect of gender, ethnicity, age, and collateral psychopathology on test results are also needed. Little research has been done on possible influences of ethnicity or collateral psychopathology, although many projects, particularly in the domain of screening, have considered how age and gender may influence results. Studies are particularly needed to contrast the use of alternative measures or the use of different cut points for adolescents with alcohol problems, as well as for older adults suffering these problems. In the area of screening, for example, it appears that the cut points for self-report measures should be somewhat lower for women and adolescents on the Alcohol Use Disorders Identification Test (AUDIT) and, although it compares quite favorably against alternative self-report screens for most age groups, it has yet to be determined if the AUDIT is preferable to measures constructed specifically for older adults or pregnant women.⁵

Research is also needed to determine if the assessment process itself has curative effects. While the primary reason for assessment is to tailor interventions to the needs, strengths, and characteristics of patients, simply exploring these issues with patients may enhance their awareness of problems and their commitment to change. Feedback based on their test results may also engage patients more fully in the treatment program by improving their understanding of the way the therapeutic regimen is tailored to address their needs and characteristics.

Investigations might also be devoted to topics such as how clinicians can incorporate assessment information into formulating an effective treatment plan. Many alcohol counselors come from educational and experiential backgrounds that have failed to provide an adequate basis in psychometric principles or in understanding the implications of assessment scores for treatment planning.

Research is also urged on a host of other applied issues related to alcohol assessment. Perhaps the major question in this regard is the optimal timing for administering various assessment measures. For the test information to be maximally useful in creating a treatment plan, it needs to be collected early in treatment. Nevertheless, responses to some measures may be heavily influenced by the acute effects of alcohol withdrawal. Early detoxifying patients may be depressed, anxious, and angry, moods that could well affect test results. Beyond this, there may be neuropsychological deficits associated with withdrawal that make it difficult to respond accurately to questions. Until rapport has been established, patients might also be less forthcoming in giving personal information or reporting accurately on their drinking and its personal consequences.

Unfortunately, very few studies have been done up to this time of the way sequencing of various measures might influence responses. In one of the few studies to consider this, it was found that if patients were asked first about their

quantity and frequency of drinking, they produced lower scores on the CAGE than if the CAGE had been given in isolation.²⁵

Because of the stringent limitations on treatment imposed by third party payers, research is needed on the relative benefits of time spent in assessment versus time spent in direct treatment activities, as well as the time required for various assessment instruments. Development of computerized administration of various measures requiring less time and use of clinical staff time are welcomed.

Tremendous strides in psychometric assessment of patients with alcohol problems have been made up to this point, and it is hoped that these efforts will continue since accurate and comprehensive assessment should lead to more effective treatment and better understanding of the findings of research on alcoholism.

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References

1. Allen, J.P., & Wilson, V. *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*, 2nd ed. Bethesda, MD: USDHHS, in press.
2. MacAndrew, C. The differentiation of male alcoholic outpatients from non-alcoholic psychiatric outpatients by means of the MMPI. *Quart J Stud Alcohol*, **26**:238–246, 1965.
3. Chang, G., Wilkins-Haus, L., Berman, S., & Goetz, M.A. The TWEAK: Application in a prenatal setting. *J Stud Alcohol*, **60**(3):306–309.
4. Sokol, R.J., Martier, S.S., & Ager, J.W. The T-ACE questions: Practical prenatal detection of risk drinking. *Am J Obstet Gyn*, **60**:863–870, 1989.
5. Allen, J.P., Reinert, D.F., & Volk, R.J. The Alcohol Use Disorders Identification Test: An aid to recognition of alcohol problems in primary care patients. *Prev Med* **33**(5):428–433.
6. Bradley, K.A. Management of alcoholism in the primary care setting. *Western J Med*, **156**:273–277, 1992.
7. Allen, J.P., Litten, R.Z., Fertig, J.B., & Sillanaukee, P. Carbohydrate deficient transferrin, gamma glutamyl transferase and macrocytic volume as biomarkers of alcohol problems in women. *Alcoholism Clin Exp Res*, **24**:492–496, 2000.
8. Allen, J.P., Litten, R.Z., Fertig, J.B., & Sillanaukee, P. Carbohydrate deficient transferrin: An aid to early recognition of alcohol abuse. *Amer J on Addictions*, **10**:24–28, 2001.
9. Monteiro, M.G., & Masur, J. Monitoring alcoholic treatment: The appropriateness of choice between gamma GT or MCV evaluation after a short time of abstinence. *Alcohol Int Biomed J*, **3**(4):223–226, 1986.
10. Sillanaukee, P., Strid, N., Allen, J.P., & Litten, R.Z. Novel biomarkers of heavy drinking. Manuscript submitted for publication.
11. Sillanaukee, P., Strid, N., Allen, J.P., & Litten, R.Z. Combining biomarkers to screen for alcohol problems. Manuscript submitted for publication.

12. Anderson, P. Alcohol and risk of physical harm. In Holder, H.D., Edwards, G. (eds.), *Alcohol and Public Policy: Evidence and issues*. New York: Oxford University Press, 1995, pp. 82–113.
13. Sobell, L.C., & Sobell, M.B. Alcohol consumption measures. In Allen, J.P., & Wilson, V. (eds.), *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*, 2nd ed. Bethesda, MD: USDHHS, in press.
14. Maisto, S.A., & McKay, J.R. Diagnosis. In Allen, J.P., & Wilson, V. (eds.), *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*, 2nd ed. Bethesda, MD: USDHHS, in press.
15. Sullivan, J.T., Sykora, K., Schneiderman, J., Naranjo, C.A., & Sellers, E.M. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale. *Br J Addict*, **84**:1353–1357, 1989.
16. Miller, W.R., Zweben, A., DiClemente, C.C., & Rychtarik, R.G. *Motivational Enhancement Therapy Manual*. Rockville, MD: USDHHS, 1992.
17. Miller, W.R., & Tonigan, J.S. *The Drinker Inventory of Consequences*. Rockville, MD: USDHHS, 1995.
18. Donovan, D. Assessment to aid in the treatment planning process. In Allen, J.P., & Wilson, V. (eds.), *Assessing Alcohol Problems: A Guide for Clinicians and Researchers*, 2nd ed. Bethesda, MD: USDHHS, in press.
19. Miller, K.J., McCrady, B.S., Abrams, D.B., & Labouvie, E.W. Taking an individualized approach to the assessment of self-efficacy and the prediction of alcoholic relapse. *J Psychopathology and Beh Assess*, **16**:111–120, 1994.
20. Peters, R.H., & Schonfeld, L. Determinants of recent substance abuse among jail inmates referred for treatment. *J Drug Issues*, **23**:101–117, 1993.
21. Reinert, D.F., & Allen, J.P. The Alcohol Use Disorders Identification Test (AUDIT): A review of recent research. *Alcohol Clin. Exp. Res.*, in press.
22. Hoffman, N.G., Halikas, J.A., Mee-Lee, D., & Weidman, R.D. *Patient Placement Criteria for the Treatment of Psychoactive Substance Use Disorders*. Washington, DC: American Society of Addiction Medicine, 1991.
23. Horn, J.L., Wanberg, K.W., & Foster, F.M. *Guide to the Alcohol Use Inventory*. Minneapolis: National Computer Systems, 1987.
24. Allen, J.P. Subtypes of alcoholics based on psychometric measures. *Alcohol Health Res World*, **20**:24–29, 1996.
25. Steinweg, D.L., & Worth, H. Alcoholism: The keys to the CAGE. *Am J Med*, **94**(5):520–523, 1993.

Biomarkers as Aids to Identification of Relapse in Alcoholic Patients

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Abstract. Since return to drinking is common in patients recovering from alcoholism, recognition of relapse should be an important component of treatment. Recurrent assessment with biochemical measures can provide clinicians with useful information on the drinking status of their patients. This chapter addresses issues surrounding the importance of early detection of relapse, describes biochemical markers that may assist in this, reviews relevant scientific investigations, and offers recommendations to researchers and clinicians.

Treatment for alcohol problems is often effective. A recent review of clinical trials, for example, concluded that fully one-third of alcohol-dependent/abusing patients maintained continuous abstinence or remained free of alcohol-related difficulties since entry into treatment a year before. Further, even nonabstinent patients drank less frequently and in lower quantities and reported fewer problems associated with alcohol consumption at 1 year follow-up.¹ In Project MATCH, for example, at 15 months from the point of treatment entry, the study sample as a whole was drinking on only about 20% or fewer days and on these days had reduced their consumption to an average of two or three drinks, whereas at the onset of treatment they had been drinking on 70 to 80% of the days and had averaged 11 to 15 drinks on those days.²

Unfortunately, a return to some level of drinking is also common among alcoholics during and shortly after treatment. Alcoholism has been termed a "chronic relapsing condition,"³ and a fundamental goal of continuing care is "early identification of initial relapses to keep them from developing into a full-blown relapse."⁴

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1. Reasons that Relapse Should Be Recognized Early

Timely recognition of relapse is desirable for several reasons. Most importantly, it may prompt needed intensification of the intervention to minimize harm from a return to drinking. Second, early recognition may disrupt an incipient pattern of drinking so that it does not become habitual and, hence, less malleable. Third, by identifying relapse soon after it has occurred, the clinician and the patient may be better able to specify the internal and external stimuli that have precipitated it, thus informing treatment strategies to more effectively counteract similar stimuli in the future. Finally, recognizing and terminating a relapse before the drinking has exacerbated may render the patient more likely to persevere in treatment.

Beyond yielding direct benefits to the patient, early detection of relapse may also strengthen the credibility of a treatment program with its referral sources. Many alcoholics enter treatment under some form of external coercion such as threats of prosecution, loss of employment, or revocation of driving privileges. Failure of treatment programs to recognize when patients are not doing well and, thereby, failure to take appropriate remedial action may undermine the confidence of those in a position to make future referrals to them.

The current chapter addresses the contribution of biochemical markers for monitoring alcohol treatment progress, reviews scientific literature on biomarkers and relapse, offers recommendations for research still needed on the topic, and makes suggestions to counselors on how they might effectively employ biomarkers in treating alcoholic patients.

2. The Role of Biomarkers in Relapse Recognition

Although alcoholism counselors generally rely solely on direct verbal questioning to determine whether or not relapse has occurred, some patients may fail to acknowledge a return to drinking. In particular, erroneous reports of abstinence are even more common among older, less educated, more psychiatrically impaired, and more alcohol-involved individuals.⁵ Inadequately trained interviewers and poor interview conditions have also been implicated as more likely to elicit invalid self-reports of drinking status.⁶

Assessment of biochemical changes can supplement patients' self-reports in identifying alcohol relapse. The unique capability of biomarkers in this regard is clearly illustrated by a recent investigation by Mundle and his colleagues.⁷ Despite having excluded from analyses those suffering major psychiatric conditions or severe liver diseases or taking medications that could elevate liver enzymes, 15% of male alcoholic outpatients who denied drinking, nevertheless, produced elevated scores on at least one of two biochemical markers usually indicative of drinking. Of note, these subjects had also been previously informed that the blood tests they would take could detect drinking and thus would probably be more likely to admit relapse than would be recovering alcoholics expecting only verbal inquiry about their drinking status. So, too, Borg et al.⁸

found that far more episodes of drinking were evidenced by elevation of 5-HTOL/H-HIAA (described below) than by self-report in male alcohol-dependent outpatients. In a particularly well-analyzed trial, Keso and Salaspuro⁹ also observed that, although clinical interviews identified some relapses not reflected by elevated biomarker scores, the converse was also true. Finally, at least two projects have also shown that biomarkers of drinking may elevate well before patients self-acknowledge relapse.^{10,11} In this latter study, nearly half of the relapses were initially identified by elevation of a highly specific drinking marker, carbohydrate deficient transferrin, in patients who had heretofore denied drinking, but further evaluation and questioning revealed that they had relapsed.

3. Desirable Qualities in a Biomarker of Relapse

Most of the qualities sought in a marker for alcohol screening are also desirable in a marker for alcohol relapse,¹² including high levels of sensitivity (i.e., accurately identifying relapses) and specificity (confirming continuing abstinence). Of these, specificity may be even more important in a relapse marker than in a screening marker since in the latter situation, false positive errors can be corrected by subsequent structured evaluation of dependence symptoms, whereas well-validated diagnostic measures of relapse are not yet available. Mislabeling an alcoholic patient in treatment as having relapsed may erode the rapport and trust between patient and therapist and vice versa.

As with screening markers, issues of cost and acceptability to the clinician and the patient also merit consideration, but the timeliness with which results must be available is somewhat less critical than for screening. Unlike in primary care settings where the patient may be seen only a single time, in alcohol treatment he or she will be seen on a continuing basis, and it would thus be possible to discuss the results of a positive laboratory test at the next session. Nevertheless, as argued above, identification of relapse as soon as possible after its occurrence still remains an important goal.

Although considerations of the time frame when a biomarker remains elevated after drinking and the level of alcohol consumption necessary to elevate it are significant issues, one should also bear in mind that the potential value of the test is also related to the nature and patterns of drinking resumption within or following treatment. For example, analyses of follow-up data from Project MATCH revealed that male patients who acknowledged having had at least one drink in the previous 30 days, in fact, averaged 118 drinks, the comparable figure for women who admitted having had at least one drink was 82,¹³ a point that should also be borne in mind in considering biomarker studies defining relapse as "any drinking."

4. Biomarkers of Relapse

Although biochemical markers have been frequently employed as measures of treatment efficacy,¹⁴ there are fewer studies exploring their potential as indicators

of relapse. When used as indicators of relapse rather than as outcome variables in clinical trials, biomarkers must have higher levels of accuracy since they are to identify individual patients rather than aggregates across an entire group. In this regard, relapse biomarkers are sometimes scored ipsatively (i.e., the patient's score at the present time is contrasted with the lowest level on the marker that he or she has achieved to date, and the patient is assumed to have relapsed if the current level exceeds this by some amount. In clinical trials, scores are computed normatively and rarely consider change within particular research subjects.) When used as relapse indicators, biomarkers are generally scored dichotomously as above or below a cutoff score. In clinical trials, they are usually scored as continuous variables. Finally, to be of maximal clinical utility, relapse markers should be repeated at reasonable intervals so that the clinician can effectively and continuously monitor the patient's progress in recovery. In efficacy trials, biomarkers are often evaluated only at baseline and at a single end point of treatment.

Several alcohol-screening markers have been evaluated for their potential to detect relapse to drinking. The most common of these is gamma-glutamyl transpeptidase (GGT). GGT elevation seems to be due to increased synthesis or accelerated release of this enzyme from damaged or dead liver cells.¹⁴ Levels of GGT generally return within the normal reference range within a month to 6 weeks of initial abstinence. The half-life of GGT is 14 to 26 days. GGT also rises in many hepatobiliary disorders, obesity, diabetes, hypertension, and hypertriglyceridemia, as well as during treatment with some medications. False negatives on GGT, are also quite common, occur in up to 60% of heavy drinkers.

Serum aminotransferases, aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT), have also been employed for relapse detection. Elevated values reflect liver damage often, although not always, related to heavy drinking. The basis of elevation seems to be abnormal hepatocellular membrane permeability.¹⁵ In its own right, ALAT is not very enlightening as an indicator of alcohol abuse, but the ratio ASAT/ALAT may yield useful information on drinking status.¹⁶⁻¹⁸ A value exceeding 2, it is assumed, reflects alcohol problems.¹⁹

High mean corpuscular volume (MCV) may result directly or indirectly from the effects of alcohol on erythroblast development.^{20,21} Unfortunately, MCV's purported slow return to reference values and lack of specificity probably reduce its potential application as a stand-alone indicator of a return to drinking.

Transferrin is an ubiquitous glycoprotein that is manufactured in the liver, circulates in blood, and facilitates iron transport. Under usual conditions, transferrin contains two carbohydrate residues and two N-linked glycans to which up to six sialic acid moieties may be attached. With heavy drinking, these terminal chains may have somewhat less carbohydrate content and thus constitute "carbohydrate deficient" transferrin (CDT).²² Sillanaukee et al.²³ recently reviewed possible mechanisms by which alcohol may reduce the carbohydrate content of transferrin.

Initially, CDT levels rise with alcohol consumption of 60 to 80 g/day that has continued for 2 or 3 weeks.²⁴ CDT has a mean half-life of 12 to 17 days if the patient ceases drinking.²⁵ False positive CDT results are rare and tend to occur only in individuals with an inborn error of glycoprotein metabolism, genetic D-variant of transferrin, very severe liver diseases such as primary biliary cirrhosis, diseases involving high total transferrin, or combined kidney and pancreas transplants.^{22,24–27} Although the sensitivities of GGT and CDT are approximately equal as screens for heavy drinking or alcohol dependence, CDT is much more specific.²⁸

End products of metabolism of the neurotransmitter serotonin include 5-hydroxytryptophol (5-HTOL) and 5-hydroxyindole-3-acetic acid (5-HIAA). Excessive alcohol consumption can alter the metabolism of serotonin and induce a higher production of 5-HTOL. Levels of 5-HTOL may remain high for a number of hours after ethanol levels in the body have returned to baseline. Thus, 5-HTOL is a marker of rather recent alcohol consumption.

Since 5-HIAA decreases as 5-HTOL increases, the ratio 5-HTOL/5-HIAA is more sensitive and specific to drinking than the raw value of 5-HTOL itself.²⁹ The ratio also corrects for urine dilution and for fluctuations in serotonin metabolism related to dietary intake of serotonin,³⁰ although it is also increased in patients taking disulfiram, calcium cyanamide, or glyburide.³¹ Helander³² has argued that the effect of aldehyde dehydrogenase inhibitors, most notably disulfiram, is simply to establish a higher comparison baseline for 5-HTOL/5-HIAA but not to preclude it from being able to signal alcohol consumption. Unlike other common relapse markers, a single episode of drinking may elevate 5-HTOL/5-HIAA.

5. Summary of Findings on Biomarkers of Relapse

The earliest investigation reporting sensitivities and specificities for biomarkers of relapse is by Shaw et al.³³ Although the research team found little value in MCV as an indicator of return to drinking, GGT accurately identified 45% of those who had relapsed and 91% of those who had, from all indications, remained abstinent. Plasma alpha amino-*n*-butyric acid (AANB), a marker no longer under active investigation, detected 50% of those who had relapsed and 97% of those who had remained abstinent. Simultaneous consideration of GGT and AANB yielded sensitivity of 75% and specificity of 86% for relapse to drinking.

Using an earlier determined cutoff of at least a 20% increase in GGT or ALAT or a 40% increase in ASAT from the values observed after 4 weeks of alcohol abstention, Irwin and his colleagues³⁴ correctly identified 100% of male patients who had engaged in drinking at some point during the past 14 days and 82% of those had refrained from drinking during the 3-month follow-up period. Excluded from the analysis were patients who were "secondary" alcoholics (i.e., had an additional major psychiatric disorder), had liver disease, or

were taking medications that could elevate their liver enzymes. Despite the intriguing results of the project, no research was located that further cross-validated or extended its findings.

Following a gap of several years since these two seminal efforts in the field, almost all subsequent relapse marker investigations have included CDT, either in isolation or in combination with one or more other markers. Table 1 presents basic design features of these studies. Some comments related to Table 1 are in order. Although as a rule, investigations have defined relapse as return to any level of alcohol use, a few have employed less stringent definitions or have considered more than one level of relapse severity. Self-report has often been the primary basis for establishing the occurrence of a relapse, but many of the projects have used the time-line follow-back technique,³⁵ the standard for collecting self-report drinking behavior, to collect the information. Interviews with collaterals believed at least somewhat aware of the patient's possible drinking, presence of alcohol in the urine or breath, and 5-HTOL have also been employed to corroborate/modify the patient's self-report.

With the exception of Project MATCH,¹³ none of the investigations published to date have provided information on how the biomarkers perform with women, either because women were not included in the trial or because their number was too small to allow gender-specific analyses.

Table II reports the sensitivities and specificities of CDT and GGT, as well as of their combination. In all instances, the combination was scored according to a simple binary inclusion rule (i.e., if the patient was in the positive range of either test, he or she was considered to have relapsed).

A few general observations may also be offered on Table 2. Although various procedures have been used to test for and quantify CDT, absolute cutoff values recommended for screening purposes by the manufacturers of the kits have usually served as the basis for identifying relapse. Separation and quantitation of GGT are less technically complex, standardized reagent kits are not used, and a wide variety of cutoffs have been used to evaluate GGT. These may be idiosyncratic to particular studies and selected to maximize validity of GGT as an index of relapse. Until GGT cutoffs are cross-validated in new samples, it is difficult to directly contrast the performance of the two markers.

Significant variation in performance of the tests across studies is evident, but the basis for this is unclear. Conceivably, differing results reflect factors such as the particular samples studied, the nature of the relapse drinking, the frequency of testing, and the quality of laboratory procedures.

Across all studies of males or males and females combined, the median sensitivity for CDT was .65 (range .33 to .92) and for GGT was .57 (range .34 to .66) with corresponding specificities of .92 (range .60 to 1.00) and .78 (range .63 to .93). Thus, although they are approximately equal in sensitivity, CDT offers an advantage in specificity. The median sensitivity for the combination of CDT and GGT in the four studies computing it was .74 (range .51 to .80), and with the median specificity also was .74 (range .65 to .90). Contrasting these values with CDT alone reflects a median gain in sensitivity of .23 and a corresponding

Table 1. Design Features of Studies Involving Carbohydrate Deficient Transferrin as a Marker of Relapse to Drinking

Study	Subjects	Relapse Definition	CDT Test	2nd Marker	Testing Times
Allen et al. ¹³ 1999	905 male alc. s. 310 female alc. s.	(1) Any dkg. (2) 5 + dks. in a day. (3) 3 days in a row of 5 dks./day	CDTect	GGT	End of mo. 15 post-treatment assignment
Berlakovich et al. ³⁶ 1999	97 alc. s. with liver transplants	Any dkg.	CDTect		1/wk for 1 mo., 2/mo. for mos. 2 and 3, 1/mo., for mos. 4–6, every 2–3 mos. for last 6 mos.
Mundle et al. ⁶ 1999	144 male alc. s. abstinent for > 3 wks.	Any dkg.	%CDT-RIA	GGT MCV	Baseline and 6 mos.
Limin et al. ³⁷ 1999	58 alc. s.	> 40 dks./2 wks.	%CDT-TIA	GGT	Not specified
Kverme et al. ³⁸ 1997	57 alc. s.	Any dkg.	%CDT-RIA	GGT	Every 2 wks.
Mitchell et al. ¹⁰ 1997	53 alc. s.	(1) 56 + dks./wk. (2) At least 1 alc. problem in last 14 days	CDTect	GGT	Every 2 wks. for 6 mos.
Schmidt et al. ³⁹ 1997	101 male alc. s.	Any dkg.	MAEC-TM	GGT	1/wk. for mo. 1, every 2 wks. for next 2 mos., every 4 wks. for last 3 mos.
Rosman et al. ¹¹ 1995	86 male alc. s.	Any dkg. (3 levels of severity)	MAEC-RIA		Baseline, every 4 wks. for 4 mos., and at 12 mos.

Abbreviations for Table

Alcs. = Alcohol dependent patients.

Wk. = Week.

Mo. = Month.

CDT = Carbohydrate deficient transferrin.

GGT = Gamma-glutamyl transferase.

MCV = Macrocytic volume.

AST = Aspartate aminotransferase.

ALT = Alanine aminotransferase.

median loss in specificity of .16. Against GGT alone, the combination produces a median gain in sensitivity of .20 and a median decrease in specificity of only .04. Adding CDT to GGT has little negative effect on specificity due to CDT's high degree of specificity. That the gain in sensitivity exceeds the loss in

Table 2. Sensitivity and Specificity for Relapse for CDT, GGT, and the Combination of CDT and GGT

Study	CDT Sens.	CDT Spec.	GGT Sens.	GGT Spec.	CDT + GGT Sens.	CDT + GGT Spec.
Allen et al. ¹³ (Males)	.56	.81	.53	.74	.77	.65
Allen et al. ¹³ (Females)	.20	.81	.31	.91	.48	.73
Berlakovich et al. ³⁶	.92	.98				
Mundle et al. ⁶	.55	.97	.50	.93	.80	.90
Limin et al. ³⁷	.43	.88	.57	.63	.70	.57
Kverme et al. ³⁸	.74	1.00	.66	.78		
Mitchell et al. ¹⁰	.90	.60	.59	.73		
Schmidt et al. ³⁹	.33	.96	.34	.77	.51	.79
Rosman et al. ¹¹	.76	.79				

specificity demonstrates that the two tests are accurately identifying somewhat different relapsing patients. Therefore, the test should probably be used in combination since the gain in sensitivity exceeds the loss in specificity.

Far less can be said with confidence about the ability of either marker to identify relapse in alcoholic women since, as noted, Project MATCH was the only study that reported findings for women. Neither test did as well with women as with men. Further, unlike the general finding that CDT performs better than GGT in men, the converse may be true in women. As for men, the combination of the two markers improves sensitivity considerably, albeit at a fairly high cost to specificity. The poorer performance of the two tests in women may at least partially reflect the fact that the women in MATCH who relapsed were still consuming only about half of the alcohol as the men who did so.¹³

Review of the studies cited in Tables I and II leads to several additional observations. Neither marker is closely associated with the reported quantity of drinking during a relapse. Mitchell et al.¹⁰ found that correlations of GGT with level of drinking were not statistically significant. Correlations with CDT were minimal to moderate.

Severity of relapse in terms of duration was slightly related to the likelihood that either or both CDT and GGT were above the cutoff.¹³ Curiously, GGT, but not CDT, demonstrated this phenomenon in the female sample. Although their sample was quite small, Rosman et al.¹¹ failed to detect this effect in male alcoholics at the CDT kit manufacturer's recommended screening cutoff value of 20 mg/L. Employment of a cutoff of 25 mg/L, however, resulted in missing about half of the minor relapses but still allowed recognition of most of the more serious ones.

Both CDT and GGT elevation were also associated with relapse when it was defined not by drinking itself, but rather by adverse consequences of drinking.¹⁰ The relationship was only slightly lower than that when drinking itself was taken as the relapse criterion.

A pronounced "heralding" effect has been reported for CDT in which relapses are often identified initially by CDT elevation and only later by patient self-acknowledgement. Rosman et al.¹¹ noted that 42% of the relapses were identified by elevation of CDT at least 28 days before the patient admitted having returned to drinking. (In these instances the relapse was identified by subsequent more intense questioning of the patient, discussion with collaterals, or discovery that the patient had been hospitalized for treatment of an alcohol-related problem.) So, too, Mitchell et al.¹⁰ noted that CDT tended to react more "briskly" than GGT to return to drinking, an observation also made by Schmidt et al.³⁹

Recent findings suggest that measuring CDT as a percentage of total transferrin, as opposed to using raw absolute CDT values, can be used to monitor abstinence in alcoholics. This strategy might be particularly helpful for relapse monitoring in recovering alcoholic women since there does not appear to be a gender effect on the sensitivity of CDT if measured as a percentage of total transferrin.⁴¹

6. Future Research Questions

Despite promising research results on biomarkers as aids to relapse identification, a variety of critical questions remain. It would be especially useful to determine the degree of possible reactivity of biomarkers in this context. To what extent does awareness that their self-report of abstinence is subject to biochemical corroboration influence drinking behavior, as well as the validity of self-report of drinking?

A second issue concerns the advisable schedule of follow-up testing with biomarkers. In that alcohol relapse is more common in initial phases of recovery than in later ones, it would seem that early testing should be conducted fairly often but could diminish in frequency as recovery progresses. Research to establish optimal schedules of testing with alternative biomarkers should consider the capabilities of the tests such as half-lives, decay curves, and dose-response relationships with consumption, as well as relapse drinking quantities and patterns. This latter issue merits particular attention since, to date, little research has been done to determine what constitutes a clinically significant relapse and this should be the criterion against which the markers are evaluated.

As noted frequently in the literature, most of the traditional markers do not perform as well in identifying drinking in women and adolescents as they do in adult males. Hence, there is a continuing need to develop markers or combinations of markers that will be more accurate for them. Further, for reasons as yet unclear, patients may respond differentially to alternative markers. As in alcohol screening markers, for relapse markers, some subjects are primarily CDT-responders, whereas others are GGT-responders.⁴² Yet another group may be MCV-responders.⁴³ It would be important to determine the reasons for differential response, so that patients might be followed with the biomarker most appropriate for them.

Most studies have evaluated biomarkers of relapse individually, although this chapter does identify five instances of their use in combination, and combinatorial use, it has been consistently found, enhances test accuracy. To date, all of the investigations have employed only an inclusionary "either/or" scoring algorithm in which it is assumed that the patient has relapsed if at least one of the markers is elevated above its screening cutoff value. Other arithmetic combinations should also be considered. For example, Sillanaukee et al.⁴⁴ developed a scoring algorithm for screening that sums weighted logarithmic scores for CDT and GGT. Curiously, the commonly reported problem of less accurate recognition of women with alcohol problems versus men with such problems did not occur when this formula was employed. Similar work is needed to develop an optimum relapse marker score.

A recent innovative study by Burke et al.⁴⁵ showed that changes of 10% in levels of CDT, although not those of GGT, were associated with changes in daily alcohol consumption by one to three drinks in males who usually consumed two to six drinks per day. This project was conducted on a nonclinical sample. If the findings are replicated in an alcohol treatment-seeking sample, it might be possible to employ CDT as a measure of treatment progress in programs or patients without a goal of total abstinence.

Some researchers^{24,42,46} have suggested that there may be a "sensitization effect" for biomarkers (i.e., alcohol consumption at lower levels may reelevate them rather than the levels originally required). Formal investigations are needed to demonstrate whether or not this phenomenon actually occurs, and, if so, the parameters of relapse drinking that would prompt such reelevation.

Although the research on biomarkers as indicators of relapse is quite positive, none of the currently available biomarkers demonstrates perfect sensitivity, or specificity and, hence, improved biomarkers must still be sought. Initial research on transdermal devices and acetaldehyde adducts is promising in this regard.

The alcohol "sweat patch" collects transepidermal ethanol for periods of at least 10 days and can identify even low levels of alcohol consumption. Additional investigation must be performed if the sweat patch is to be clinically applied to indicate relapse in alcoholic patients. A more promising transdermal approach involves using a sensor that detects ethanol vapor at the surface of the skin and produces a signal current proportional to the concentration of alcohol.⁴⁷ The device can also monitor continuous skin contact making it evident to the clinician reviewing results if the device has been removed. Current research efforts are designed to miniaturize the apparatus.

Acetaldehyde, a breakdown product of alcohol, can form stable adducts with a number of compounds including proteins such as albumin and hemoglobin.⁴⁸⁻⁵⁰ Adduct levels have been considered a potential marker of heavy drinking.⁵¹ Studies have shown that whole blood associated acetaldehyde levels increased in mice fed ethanol for 24 hours afterward.^{52,53} With 9 days of abstinence, the levels declined to control values.⁵² Although these observations have also been confirmed in humans, measurement of acetaldehyde adducts in blood remains difficult due to their low quantities and the procedural difficulty of measurement. There is, as yet, no commercial assay of low to moderate complexity.

7. Recommendations to Clinicians

Granted current findings on biomarkers and relapse, some recommendations can be offered to clinicians who treat patients for alcohol dependence.

Initial biomarker testing should be done as quickly as possible after entry into treatment. Specification of the biomarkers on which the patient is elevated and which begin to decline with abstinence will suggest the markers on which the patient can be primarily monitored. More than one biomarker may be used, especially if it is not apparent to which the patient is most responsive. The combination of CDT and GGT is probably best, although a combination such as 5-HTOL and CDT may also be useful if a commercial kit becomes available and the single instance of use of CDT, GGT, and MCV yielded quite promising results.⁷

Tests conducted early in outpatient recovery should probably be fairly frequent, perhaps every 2 weeks or so since this is a period of particularly high relapse vulnerability. The frequency of testing can diminish as the patient is successful with recovery for longer periods of time. It would seem reasonable that after perhaps 3 months or so of abstinence that the frequency of testing would diminish to once a month unless there is a suspicion of relapse to drinking, such as missed appointments, family complaints, increased blood pressure, or medical signs.

Current biomarkers should be contrasted with both established screening values, as well as with the lowest levels of the test achieved to date. As observed earlier, a few studies^{8,40,46} have found that substantial within-individual reelevation of the biomarker is a more accurate index of relapse than scoring the test simply as above cutoff, whereas others have opted to characterize the markers as simply above or below the normative screening cutoff value.

Patients should be given feedback on biomarker scores in an empathetic manner. To enhance both the reinforcement and the motivational values of the scores, it might be helpful to sequentially plot scores on a grid to incorporate into feedback sessions that follow each testing.

Most importantly, in considering biomarkers, clinicians should be aware of the likelihoods and sources of false positives and false negatives on them. Although biomarkers can provide valuable information, they should be considered in the context of all available sources of information on drinking status.

References

1. Miller, W.R., Walter, S.T., & Bennett, M.E. How effective is alcoholism treatment in the United States. *Journal of Studies on Alcohol* 62: 211–220, 2001.
2. Fuller, R.K. & Allen, J.P. Patient-to-treatment matching. In Zernig, G., Saria, A., Kurz, M.D., & O’Malley, S.S. (eds.), *Handbook of Alcoholism*. New York, CRC Press, 2000, pp. 363–368.
3. Connors, G.J., Maisto, S.A., & Donovan, D.M. Conceptualizations of relapse: A summary of psychological and biological models. *Addiction*, 91(suppl): 5–14, 1996.
4. Donovan, D.M. Continuing care. In Miller, W.R. & Heather, N. (eds.), *Treating Addictive Behaviors*. Plenum Press, 1996, pp. 317–336.
5. Babor, T.F., Steinberg, K., Anton, R., & Del Boca, F. Talk is cheap: Measuring drinking outcomes in clinical trials. *Journal of Studies on Alcohol*, 61: 55–63, 2000.

6. Mundle, G., Ackermann, K., & Mann, K. Biological markers as indicators for relapse in alcohol-dependent patients. *Addiction Biology*, 4: 209–214, 1999.
7. Mundle, G., Ackermann, K., Gunther, A., Munkes, J., & Mann, K. Treatment outcome in alcoholism—A comparison of self-report and the biological markers carbohydrate-deficient transferring and γ -glutamyl transferase. *European Addiction Research* 5: 9–96, 1999.
8. Borg, S., Helander, A., Carlsson, Voltaire, A., & Brandt Hogstrom, A.M. Detection of relapses in alcohol-dependent patients using carbohydrate-deficient transferrin: Improvement with individualized reference levels during long-term monitoring. *Alcoholism Clinical and Experimental Research* 19(4): 961–963, 1995.
9. Keso, L. & Salaspuro, M. Comparative value of self-report and blood tests in assessing outcome amongst alcoholics. *British Journal of Addictions* 85: 200–215, 1990.
10. Mitchell, C., Simpson, D., & Chick, J. Carbohydrate deficient transferrin in detecting relapse in alcohol dependence. *Drug and Alcohol Dependence* 48: 97–103, 1997.
11. Rosman, A.S., Basu, P., Galvin, K., & Lieber, C.S. Utility of carbohydrate-deficient transferrin as a marker of relapse in alcoholic patients. *Alcoholism Clinical and Experimental Research* 19(3): 611–616, 1995.
12. Anton, R.F., Litten, R.Z., & Allen, J.P. Biological assessment of alcohol consumption. In Allen, J.P. & Columbus M. (eds.), *Assessing Alcohol Problems*. Bethesda, MD: USDHHS, 1995, pp. 31–40.
13. Allen, J.P., Sillanaukee, P., & Anton, R. Contribution of carbohydrate deficient transferrin to gamma glutamyl transpeptidase in evaluating progress of patients in treatment for alcoholism. *Alcoholism Clinical and Experimental Research* 23(1): 115–120, 1999.
14. Allen, J.P., Litten, R.Z., Sillanaukee, P. & Strid, N. The role of biomarkers in alcohol medication trials. *Alcoholism Clinical and Experimental Research* (in press).
15. Zimmermann, H.J. & West, M. Serum enzyme levels in the diagnosis of hepatic disease. *American Journal of Gastroenterology* 40: 387–404, 1963.
16. Reichling, J.J. & Kaplan, M.M. Clinical use of serum enzymes in liver disease. *Digestive Disorders Science* 33: 1601–1614, 1988.
17. Kontinen, A., Hartel, G., & Louhija, A. Multiple serum enzyme analysis in chronic alcoholics. *Acta Medica Scandanavica* 188: 257–264, 1970.
18. Skude, G. & Wadstein, J. Amylase, hepatic enzymes and bilirubin in serum of alcoholics. *Acta Medica Scandanavica* 201: 53–58, 1977.
19. Matloff, D.S., Selinger, M.J., & Kaplan, M.M. Hepatic transaminase activity in alcoholic liver disease. *Gastroenterology* 78: 1389–1392, 1980.
20. Buffet, C., Chaput, J., Albuison, F., et al. La macrocytose dans l'hepatite alcoolique chronique histologiquement prouvee. *Archives Francaises Medicale Applications Digest* 64: 309–315, 1975.
21. Whitehead, T.P., Clarke, C.A., Bayliss, R.I., & Whitfield, A.G. Mean red cell volume as a marker of alcohol intake. *Journal of the Royal Society of Medicine* 78: 880–881, 1985.
22. Stibler, H. & Borg, S. The value of carbohydrate-deficient transferrin as a marker of high alcohol consumption. In Kuriyama, K., Takaya, A., & Ishii, H. (eds.), *Biochemical and Social Aspects of Alcohol and Alcoholism*. Amsterdam: Elsevier Science, 1988, pp. 503–506.
23. Sillanaukee, P., Strid, N., Allen, J.P., & Litten, R.Z. Possible reasons why heavy drinking increases carbohydrate-deficient transferrin. *Alcoholism Clinical and Experimental Research* 25(1): 34–40, 2001.
24. Stibler, H. Carbohydrate-deficient transferrin in serum: A new marker of potentially harmful alcohol consumption reviewed. *Clinical Chemistry* 37: 2029–2037, 1991.
25. Bean, P. & Peter, J.B. Allelic D variants of transferrin in evaluation of alcohol abuse: Differential diagnosis by isoelectric focusing-immunoblotting-laser densitometry. *Clinical Chemistry* 40: 2078–2083, 1994.
26. Niemela, O., Sorvajarvi, K., Blake, J.E., et al. Carbohydrate-deficient transferrin as a marker of alcohol abuse: Relationship to alcohol consumption, severity of liver disease, and fibrogenesis. *Alcoholism Clinical and Experimental Research* 19: 1203–1208, 1995.
27. Arndt, T., Hackler, R., Miller, T., Kleine, T.O., & Gressner, A.M. Increased serum concentration of carbohydrate deficient transferrin in patients with combined pancreas and kidney transplantation. *Clinical Chemistry* 43: 344–351, 1997.

28. Litten, R.Z., Allen, J.P., & Fertig, J.B. γ -glutamyltranspeptidase and carbohydrate deficient transferrin: Alternative measures of excessive alcohol consumption. *Alcoholism Clinical and Experimental Research* 19(6): 1541–1546, 1995.
29. Voltaire, A., Beck, O., & Borg, S. Urinary 5-hydroxytryptophol: A possible marker of recent alcohol consumption. *Alcoholism Clinical and Experimental Research*, 16: 281–285, 1992.
30. Feldman, J.M. & Lee, E.M. Serotonin content of foods: Effect on urinary excretion of 5-hydroxyindoleacetic acid. *American Journal of Clinical Nutrition* 42: 639–643, 1985.
31. Borg, S., Beck, O., Helander, A., Voltaire, A., & Stibler, H. Carbohydrate-deficient transferrin and 5-hydroxytryptophol: Two new markers of high alcohol consumption. In Litten, R.A. & Allen, J.P. (eds.), *Measuring Alcohol Consumption*. Totowa, NJ, Humana Press, pp. 149–155.
32. Helander, A. Monitoring relapse drinking during disulfiram therapy by assay of urinary 5-hydroxytryptophol. *Alcoholism Clinical and Experimental Research* 22: 111–114, 1998.
33. Shaw, S., Worner, T.M., Borysow, M.F., Schmitz, R.E., & Lieber, C.S. Detection of alcoholism relapse: Comparative diagnostic value of MCV, GGTP, and AANB. *Alcoholism Clinical and Experimental Research* 3: 297–301, 1978.
34. Irwin, M., Baird, S., Smith, T.L., & Schuckit, M. Use of laboratory tests to monitor heavy drinking by alcoholic men discharged from a treatment program. *American Journal of Psychiatry* 145: 5, 1988.
35. Sobell, L.C. & Sobell, M.B. Alcohol consumption measures. In Allen, J.P. & Columbus, M. (eds.), *Assessing Alcohol Problems*. Bethesda, MD USDHHS, 1995, pp. 55–74.
36. Berlakovich, G.A., Windhager, T., Freundorfer, E., Lesch, O.M., Steininger, R. & Mulbacher, F. Carbohydrate deficient transferrin for detection of alcohol relapse after orthotopic liver transplantation for alcoholic cirrhosis. *Transplantation* 67(9): 1232–1235, 1999.
37. Limin, S., Jarvis, D.R., Chick, J., & Simpson, C.D. Limitations of CDT and GGT in detecting relapses in patients attending an alcohol problems clinic. *Scottish Medical Journal* 44: 140–142, 1999.
38. Kverme, A.T. & Buchmann, M. Carbohydrate deficient transferrin (CDT) and gamma-glutamyltransferase (GGT) in diagnosis and monitoring of abstinence among alcohol abusers. *Hepatology* 26 (4 Part 2): 544A, 1997.
39. Schmidt, L.G., Schmidt, K., Dufeu, P., Ohse, A., Rommelspacher, H., & Muller, C. Superiority of carbohydrate-deficient transferrin to gamma-glutamyltransferase in detecting relapse in alcoholism. *American Journal of Psychiatry* 154(1): 75–80, 1997.
40. Myrick, H., Henderson, S., & Anton, R.F. Utility of a new assay for carbohydrate-deficient transferring to monitor abstinence during a treatment outcome study. *Alcoholism Clinical and Experimental Research*, in press.
41. Anton, R.F., Lieber, C., & Tabakoff, B. (for the CDTECT Study Group). Carbohydrate deficient transferrin (CDT) and gamma-glutamyltransferase for the detection and monitoring of alcoholics. Manuscript submitted for publication.
42. Behrens, U.J., Worner, T.M., & Lieber, C.S. Changes in carbohydrate-deficient transferrin levels after alcohol withdrawal. *Alcoholism Clinical and Experimental Research* 12(4): 539–544, 1988.
43. Monteiro, M.G. & Masur, J. Monitoring alcoholism treatment: The appropriateness of choice between γ GT or MCV evaluation after a short time of abstinence. *Alcohol* 3: 223–226, 1986.
44. Sillanaukee, P., Massot, N., Jousilahti, P., Vartiainen, E., Poikolainen, K., Olsson, U., & Alho, H. Enhanced clinical utility of γ -CDT in a general population. *Alcoholism Clinical and Experimental Research* 24(8): 1202–1206, 2000.
45. Burke, V., Puddey, I.B., Rakic, V., Swanson, N.R., Dimmitt, S.B., Beilin, S.B., Ching, S., & Beilby, J.P. Carbohydrate-deficient transferrin as a marker of change in alcohol intake in men drinking 20 to 60 g of alcohol per day. *Alcoholism Clinical and Experimental Research* 22:1973–1980, 1998.
46. Anton, R.F., Moak, D.H., & Latham, P. Carbohydrate deficient transferrin as an indicator of drinking status during a treatment outcome study. *Alcoholism Clinical and Experimental Research* 20(5): 842–846, 1996.
47. Swift, R.M., Martin, C.S., Swette, L., LaConti, A., & Kackley, N. Studies on wearable, electronic, transdermal alcohol sensor. *Alcohol Clin Exp Res* 16: 721–725.
48. Collins, M.A. Acetaldehyde and its condensation products as markers in alcoholism. *Recent Developments in Alcohol* 6: 387–403, 1988.

49. Goldberg, D.M. & Kapur, B.M. Enzymes and circulating proteins as markers of alcohol abuse. *Clinica Chimica Acta*. 226: 191–209, 1994.
50. Niemela, O. Aldehyde-protein adducts in the liver as a result of ethanol-induced oxidative stress. *Frontiers In Bioscience* 4: 506–513, 1999.
51. Tsukamoto, S., Kanegae, T., Isobe, E., Hirose, M., & Nagoya, T. Determinations of free and bound ethanol, acetaldehyde, and acetate in human blood and urine by headspace gas chromatography. *Nihon Arukoru Yakubutsu Igakkai Zasshi* 33: 200–209, 1988.
52. Peterson, C.M. & Scott, B.K. Studies of whole blood associated acetaldehyde as a marker for alcohol intake in mice. *Alcoholism Clinical and Experimental Research* 13: 845–848, 1989; Anton, R.F., Moak, D.H., & Latham, P. Carbohydrate-deficient transferrin as an indicator of drinking status during a treatment outcome study. *Alcoholism Clinical and Experimental Research* 20(5): 841–846, 1996.
53. Pantoja, A., Scott, B.K., & Peterson, CM. Studies of urine-associated acetaldehyde as a marker for alcohol intake in mice. *Alcohol* 8: 439–141, 1991.

Advances in Research Design and Analysis for Alcohol Treatment

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In recent years, both alcohol treatment research and alcohol research methods have advanced significantly. The development of new therapies, often combining multiple components, has triggered a need for complex, ambitious studies. At the same time, there have been methodological developments in several areas that, in principle, should allow us to conduct studies more effectively and allow us to draw more accurate conclusions from these studies. This chapter is divided into two major sections: (1) research design and implementation and (2) data analysis. Within each of these two major topics, there is a review of the current state of the art and comments on opportunities for further advances.

1. Research Design and Implementation

Bias is always a concern in treatment research (Cochran, 1983; Wainer, 1986). It is of particular concern in alcohol treatment research since we believe that a variety of biological, psychological, and social factors may affect treatment outcome. The likelihood that treatment groups are biased in known or unknown ways increases as the number of potential confounding variables increases. Although simple randomization ensures zero bias if the sample size is infinite, it can easily produce unbalanced samples in the range of sample sizes typically used by alcohol treatment researchers (Wei, 1978). Therefore, methods such as urn randomization or balancing on propensity scores, which minimize the probability of imbalance on a set of known predictors, have become increasingly popular. Urn randomization is a form of randomization that favors the production of equivalent treatment groups (Stout, Wirtz,

Carbonari, & Del Boca, 1994). Stratification on propensity scores (see, for example, Dehejia & Wahba, 1999) is usually done during an analysis to equate, approximately, comparison groups with regard to known confounding variables. These methods represent an improvement over previous practice, but they continue to have important limitations, and their behavior needs to be studied parametrically to provide better guidance to applied researchers.

1.1. Nonrandomized Designs

There is a continuum from classical "efficacy" studies in which considerable effort is invested to ensure internal validity (treatment impact under conditions ideally suited to maximizing such impact) to "effectiveness" studies in which the focus is shifted more toward external validity (treatment impact under real-world conditions). There has been concern in the research literature that treatments that appear to have significant impact in research settings may not have comparable impact when delivered in everyday clinical practice. There are well-known biases, however, that can affect the comparison of differentially treated cases in naturalistic settings (see, for example, D'Agostino, 1998; Wen & Kramer, 1999). It is commonplace to find, for example, that treatments that have known positive effects based on randomized trials appear to have no effect, or negative effects, in naturalistic studies. This bias arises because when treatment is not controlled; the cases that have the worst prognoses are the most likely to receive treatment, and the treatment effects are not sufficiently strong to overcome the bias. [See, for example, an analysis of whether fluoxetine is associated with elevated suicide risk. (Leon, Keller, Warshaw, Mueller, Solomon, Coryell, & Endicott, 1999.)] As discussed above, propensity score methods are the state of the art in attempting to ameliorate these biases, but they have important limitations that have only partially been overcome (D'Agostino and Rubin, 2000). Perhaps the most important limitation of propensity score methods is their inability to compensate for unknown confounding variables or an inadequate specification of the function relating the known confounders to outcome. There is, however, research on extending propensity methods to expand their applicability (Rosenbaum, 2001; Rubin & Thomas, 2000).

One way to view the issue of efficacy versus effectiveness is to see it as a special case of the problem of replicability: under what conditions can a finding observed in one setting be replicated in different settings? Since there have been failures to replicate research findings in other research settings, it is not surprising that there may be failures to replicate findings when research treatments are applied in clinical settings. The presence of site by treatment interactions in Project MATCH also provides a warning that replicability cannot be taken for granted (Project MATCH Research Group, 1997). Further research targeted at understanding the conditions under which replicability of treatment effects can and cannot be expected is needed.

1.2. Research Efficiency

Though efficiency is not a primary consideration in research design, resources are always limited, and therefore attention needs to be paid to making the best use of those resources. Research practices should be reviewed periodically to determine whether their benefits are commensurate with their costs. Below, we consider several categories related to efficiency issues.

1.2.1. Power Analysis. Because treatment research studies can involve complex statistical analyses, it can be difficult to estimate the statistical power of proposed studies. Poor estimates of power can lead to higher research costs, as investigators plan conservatively, and also can rob the field of valid results if studies are too small because of overly optimistic sample size estimates. Basic methods such as those exemplified in Cohen (1988) have been widely used for some time; however, there have been notable advances in the technology for supporting power analysis.

Recently developed methods for power analysis in the context of the general linear multivariate model (GLMM) can be adapted with relative ease to repeated measures applications (Muller, LaVange, Ramey, & Ramey, 1992). However, to the degree that they substitute point estimates from historical data sets or informed guesses of the investigator for the true model parameters, even these state-of-the art power analyses fail to reflect fully the uncertainty about the effect size. Embedding the power calculations in a sensitivity analysis, such as that conducted by Muller et al. (1992), only partly addresses such concerns, since the number of parameter combinations considered is typically small and the design matrix is taken as fixed.

It is possible to use Bayesian methods to incorporate uncertainty about effect sizes into power calculations. In principle, one can derive the joint posterior distribution of all model parameters, given historical data and/or subjective beliefs of the investigator. This information can then be used to simulate from the predictive distribution of all future observables (responses and covariates) for which the power of the classical test can then be calculated using standard methods, for example, Geisser (1993). As a result, the combination of Bayesian simulation and frequentist evaluation would allow investigators to report a range of power estimates consistent with their initial state of knowledge about the noncentrality parameter (effect size), and the optimal sample size could be determined to maximize the probability that the study will be adequately powered. This latter approach has found applications in the design of group sequential clinical trials, for example, Choi (1985), and could be adapted to treatment research.

One caveat for the more advanced methods for power analysis is that taking full advantage of these methods typically requires more information and technical consultation than the older methods. This is especially true for longitudinal studies, for which realistic power analyses, in principle, require information

about the way treatment effects (and therefore the effect size) grow and/or decay over time. Clinical investigators have often overlooked this factor in planning studies.

1.2.2. Confirmation of Drinking Status. In recent years, the practice of "confirming" drinking status by biochemical means or informant reports has been widespread in treatment research studies. These means of verification of drinking status have important practical drawbacks (notably the staff time and other expenses for obtaining the supplementary data), and rates of missing data can be high. Some of the most popular measures, notably liver function measurements, also have high false negative rates. Although combinations of multiple markers may have promise (see, for example, Allen, Litten, Fertig, & Sillanaukee, 2000), from a statistical point of view, low sensitivity is a major drawback that can substantially limit the power to detect treatment effects. It has been argued, however, that even if drinking confirmation measures are weak, it still can be valuable to obtain them because they offer a "bogus pipeline" that can help convince participants to report more accurately. There do not seem to be adequate data, however, to support or refute the bogus pipeline model. Methodological research is needed, therefore, to determine the circumstances under which bogus pipeline effects are observed and how these might be magnified.

1.2.3. Burden on Research Participants. Participants in treatment studies are typically called on to cooperate in research assessment procedures that over the years have become increasingly lengthy. The conduct of complex multivariate studies necessarily involves obtaining a wide range of information; however, there are important obvious and subtle costs for these lengthy assessment procedures. The onerousness of research assessments seems likely to affect willingness to participate in studies and also willingness to continue participation after initial consent is obtained. Payments to research subjects may in part offset the burden, but high subject payments will be an incentive only to some sectors of the population, leading to the possibility of subtle biases in the populations studied. Furthermore, high payments may be perceived as coercive. There is also reason to be concerned about the quality of research data obtained toward the end of an hours-long assessment procedure. More methodological research aimed at finding the best balance between subject participation and research needs is required.

1.3. Study of Multicomponent Therapies

It now seems accepted that alcohol treatments must be complex, multicomponent entities. In studies where pharmacotherapies are the focus, there have been findings that these therapies work most efficaciously in the context of a psychosocial intervention (see, for example, O'Malley, Jaffe, Chang, Schottenfeld, Meyer, & Rounsvville, 1992). Psychosocial therapies themselves are complex in that some give and take with the clients, and therefore explicit or implicit branching rules for dealing with unexpected issues raised by those clients, is essential. Some researchers also argue that long-term social interaction is an important component

in recovery for at least some alcohol clients; such long-duration treatment/maintenance protocols can be difficult to standardize (Stout, Rubin, Zwick, Zywiak, & Bellino, 1999). Although manualization of therapies is now a routine requirement in treatment studies (see, for example, NIAAA, 1994), it is not clear that our current approaches to describing treatment do justice to the dynamics of treatment, especially treatment that occurs across spans of months or even years. There is, therefore, a need for studies on dynamic clinical processes to understand better the nature of the interaction between client and treatment providers and to understand what aspects of this interaction may be associated with better versus worse overall outcomes.

On a related topic, it is only in recent years that the practice of studying the putative causal mechanisms underlying treatment effects has become widespread (NIAAA, 2001). Most such studies of causal chains are still crude. Since treatment effects, even when found statistically significant, are usually still relatively weak, understanding why treatments fail is a critical function of treatment research. Statistically, methods for studying very long and complex sequences of interactions (perhaps hundreds of events in a sequence) are not as well developed as those for studying other kinds of problems. Methods such as Markov chains may be suitable for some purposes, but analyses based on models for dynamic decision-making may have more promise (see below).

1.4. Replicability and Site Differences

One of the major methodological findings of Project MATCH was the presence of substantial site by treatment interactions; the rank order of treatments by outcome varied from site to site (Project MATCH Research Group, 1997). The presence of such interactions in a well-controlled multisite study suggests that treatments that we have believed are the same across settings are not necessarily identical. Several implications flow from this. First, it heightens the importance of replicating promising research findings in new settings. In Project MATCH, there was strong central supervision of treatment and extensive measurement of treatment process, and even under those circumstances, treatment main effects did not generalize across sites. In the normal situation where central treatment supervision is not present, we certainly can no longer take for granted the generalizability of treatment research findings. Second, research is needed to examine why treatments that seem promising in one setting do poorly in other settings. Understanding these reasons will help us to improve the replicability of research findings and also will provide important clues about how treatment should be implemented for maximum effectiveness.

1.5. Longitudinal Research Issues

Most treatment outcome studies are longitudinal, at least over a few months. Nonetheless, empirically based methodological guidance on basic parameters of follow-up research is minimal or lacking. Basic questions for which empirically justifiable answers are lacking include (1) how long do we

need to follow subjects? (2) what are the optimum intervals for follow-up interviews? (3) how can we maximize research retention? The answers to such questions typically vary from study to study because different investigators have established different trade-offs between research cost (number of interviewers, frequency of interviews, length of interviews), acceptable data quality (follow-up rate, depth of data, tolerance for missing individual forms), and the nature of the information about treatment effects that the study yields (level of detail about drinking or other outcome measures, duration of treatment effects, confirmation of drinking and functioning status). Clearly, further methodological research on longitudinal research practices is needed.

1.6. Outcome and Utility

The measurement of outcome continues to be an area of contention. There is general dissatisfaction with essentially all of the measures in common use (see, for example, Babor, Longabaugh, Zweben, Fuller, Stout, Anton, & Randall, 1994). Some advanced statistical techniques may ameliorate some of the disadvantages of these measures (see below), but we still lack a framework for guiding researchers' choices of measures. Much of the research in the field uses what can be called "bottom line" measures that summarize drinking behavior at a global level (e.g., percentage of days abstinent, drinks per drinking day, composite outcome). Although such measures probably are valuable in making decisions about overall efficacy, they are relatively insensitive to certain specific kinds of postulated treatment effects. Alternative measures of drinking behavior such as event duration measures are more directly related to postulated treatment effects and therefore have more power to detect these effects (Allison, 1984). To make the fullest use of these techniques, however, preliminary research must address such issues as the optimum way to define different kinds of events (see, for example, Stout, 2000).

Other methodological issues around outcome assessment remain unresolved. Treatment outcome studies typically focus on measures of drinking because it is believed that improvement in drinking precedes improvement in other areas of functioning. From the view point of social utility, however, it is the other areas of functioning that are the most important. Though it is often found that drinking behavior is correlated with functioning over long periods of time, the magnitude of the correlations varies widely. Correlations found between drinking and health costs have been unexpectedly low in some studies (Holder, Cisler, Longabaugh, Stout, Treno, & Zweben, 2000). Therefore, further research is needed on the relationships between drinking, functioning, and costs over time, and on the variables that may moderate these relationships.

2. Issues in the Analysis of Treatment Data

This section is divided into two parts. In the first, we focus on a set of statistical methods that have significant promise for application to problems in

alcohol treatment research. In the second, we discuss quantitative methods that may require substantial development work before they can properly be applied to treatment research problems.

2.1. Underutilized Statistical Methods

In recent years, several statistical methods originally developed in the 1970s have begun to find application in alcohol treatment studies. Latent growth models, structural equation models, and survival models fall into this category (Carbonari, Wirtz, Muenz, & Stout, 1994). Latent growth models are especially useful for studying outcome in longitudinal studies where spotty missing data and loss to follow-up may occur (Bryk & Raudenbush, 1992). They also are useful in certain contexts for studying the effects of time-varying covariates such as levels of stress on outcome over time. Structural equation models can be employed to study associations among imperfectly measured quantities and also to study change over time where behavior is sampled at fixed, known intervals (MacCallum & Austin, 2000; Musil, Jones, & Warner, 1998). Such models can be especially useful in testing causal chain predictions (NIAAA, 2001). Event history (survival) models are typically used to study outcome event (e.g., relapse) patterns over time. Transition (Markov) models are used for similar applications (Harris & Albert, 1991). The range of uses of event history models in alcohol treatment research has, however, been limited. For example, there have been few, if any, applications in which time-varying covariates have been used to examine the association over time between stress levels and drinking, although stress is an important component in many models of relapse. In part, technical issues limit the application of these methods to studying alcohol data (e.g., how best to define events such as "drinking episodes"; see Stout, 2000). In large degree, however, the low rate of applying these and other models listed above seems to be a function of slow technology transfer.

We now turn to some less well-known statistical procedures that deserve wider use in treatment research.

2.1.1. Generalized Estimating Equations. Outcome measures used in treatment research often exhibit statistical properties that are undesirable in the context of analyses using linear modeling approaches (regression, analysis of variance) in which normality assumptions typically are required. Methods have been developed, however, that can deal more gracefully with data that can be thought of as counts, as binary indicators, or that are simply very skewed. For example, drinks per drinking day (DDD) can be thought of as a count whose distribution for a single individual can (at least under some circumstances) be described by a Poisson or gamma model. In other circumstances, investigators may prefer to work with variables such as relapsed versus not relapsed, a binary variable that can be taken to have a Bernoulli distribution.

In the past, lack of appropriate software for fitting Poisson and binomial regression models led researchers to use a continuous normal approximation

to transformations of the discrete outcome designed to stabilize its variance, such as taking the square root of a count or the arcsine square root of a proportion. The advent of generalized linear modeling (GLM) software, such as SAS PROC GENMOD, has made approximations of this nature unnecessary, allowing us to fit both DDD and relapse status data in their original scale, instead of relying on normality assumptions. Further, the incorporation of an overdispersion parameter in standard GLM software allows us to capture part of the between-individual variability in drinking rates and the probability of binge drinking, without having to model the heterogeneity explicitly. However, in a longitudinal study, individuals are measured repeatedly over time, thus invalidating the independence assumption that underpins the GLM framework.

The need to simultaneously accommodate within-subject dependence and between-subject heterogeneity led Liang and Zeger (1986) to propose a generalized estimating equation (GEE) approach to inference. Essentially, GEE equations are modifications of the GLM score equations, which incorporate assumptions about the within-individual correlation structure of the data without requiring the specification of the entire joint distribution, a task that can be overly ambitious for multivariate discrete data. Further, GEE software replaces the model-based estimate of the covariance matrix of the regression coefficients by an empirical estimate that uses the residuals from the model. It can be shown that this "sandwich" estimator of the covariance matrix, as it is often called, is consistent, provided that the model for the mean of the observations has been correctly specified, even when the user misspecifies the correlation structure of the data.

Typically, the GEE analysis is performed under a variety of models for the covariance structure, the sign and magnitudes of the regression coefficients are checked for consistency, and those coefficients that vary little among models are singled out as robust to covariance misspecification. The remaining ones are marked out as unstable. With data such as one encounters in the alcohol treatment literature, three correlation structures that are typically employed are (1) independence, (2) exchangeable correlation, and (3) discretization of an exponentially decaying correlation model. The independence model at first seems hardly tenable for describing the within-individual correlation structure. Still, the robustification of the model-based estimate of the covariance matrix of the regression coefficients results in tests that have true significance levels closer to the nominal value than the Wald tests employed in a GLM analysis. Typically, GEE inflates the estimates of the standard errors of the coefficients, resulting in robust Z scores that are smaller than their naive Z equivalents and, therefore, in more conservative tests. The exchangeable correlation model, on the other hand, assumes that any two episodes within the same individual are equally correlated, irrespective of their separation in time. Though more tenable than the independence model, it lacks the theoretical appeal of an exponentially decaying correlation structure, under which the within-individual episodes are taken to be positively correlated and the strength of their relationship decreases with time. When drinking episodes are equispaced in time, the exponentially decaying correlation simplifies to the familiar first-order autoregressive AR(1)

model. An extensive presentation of these methods can be found in Diggle, Liang, and Zeger (1994).

GEE regression coefficients are often termed population-averaged (PA) to distinguish them from the subject-specific (SS) coefficients produced by random effects models. As explained in Zeger, Liang, and Albert (1988), PA coefficients are attenuated relatively to their SS counterparts because they answer questions pertaining to groups rather than individuals, for example, what is the difference in the proportions of relapsed drinkers on naltraxone and those taking acamprosate, rather than what is the probability of relapse when an alcoholic on naltraxone switches to acamprosate.

GEE methods are a good example of the way modern computational statistics can contribute to alcohol research. These methods, which are considerably more robust than classical linear models and allow us simpler, more direct answers to clinical questions, are possible only because of the availability of high-speed computers. Though there are important technical complexities involved in using these methods, their attractive properties make it likely that they will be widely used in future alcohol treatment outcome studies.

2.1.2. Mixture Models for Drinking Rate Data. GEE methods make possible improved analyses using nonnormal error models, as described above, but there are still reasons to be concerned with this approach. An alternative way to look at such data assumes that the population under study is a mixture of two subpopulations—one a group of abstainers (who create a point mass at zero drinks) and the other a group of drinkers whose consumption is Poisson distributed, including some who consume zero drinks by chance (see, e.g., Lambert, 1992; Mullahy, 1986). When we have heterogeneity like this in the outcome distribution, the best possible analysis would incorporate and model this heterogeneity directly. If we knew with certainty the identity of the abstainers or the drinkers, we could analyze the two populations separately. Typically, however, the classification of each subject is unknown, and the probability of being an abstainer is itself also a parameter of interest. In that case, Expectation-Maximization (EM) algorithms must be used to fit this two-component (abstainers and drinkers) mixture model. Methods for doing such analyses at one outcome time are currently available; however, methods for performing such analyses across multiple times remain under development.

It may be necessary to extend the mixture-of-populations idea even further. The population of drinkers may itself be heterogeneous, so that a standard Poisson model is inadequate for that subgroup. In such situations, zero-inflated negative binomial models are an option for coping with overdispersion in counts relative to a Poisson process.

2.2. Statistical Methods Requiring Further Development

There is some overlap between the previous section and this one. We mentioned, for example, that there are several technical and practical challenges

involved in achieving the full potential of event history models in treatment research. Nonetheless, it is useful to distinguish situations where technology transfer is the primary obstacle from situations where technology development is an issue.

2.2.1. Missing Data Methods. Better ways to deal with missing data are badly needed in alcohol research. There is a very extensive literature in statistics on methods for conducting valid statistical analyses in the presence of missing data (see, for example, Little & Rubin, 1987). The suitability of many of the techniques described in this literature for alcohol research applications is, however, dubious. Much of the statistical literature focuses on methods suitable for situations in which the assumption of ignorability is tenable (that is, the assumption that data are missing for reasons that have no connection to the processes that affect outcome). Though there probably are some "ignorable" missing data in alcohol research studies, there is empirical evidence that data missing for reasons that are very likely to be related to outcome are probably commonplace (Stout, Brown, Longabaugh, and Noel, 1996). The common practice of testing for a few baseline differences between followed and not-followed cases has at least two major flaws: (1) the power to detect differences is often low because of limited sample sizes and (2) the variables incorporated into these tests (usually background variables) often are not those most likely to be associated with the mechanisms that lead to missing data. In real clinical studies, multiple missing data mechanisms are likely to be at work. Sophisticated methods for understanding how these heterogeneous missing data mechanisms may affect estimated outcomes remain to be developed.

2.2.2. Multiple Event History Models. Alcohol treatment researchers are often interested in both survival analysis of the time to the initiation of drinking (or problem drinking) and in the time from that point until drinking ceases and something like remission is achieved. These two quantities affect overall outcome, but the treatment methods that affect one would not necessarily be expected to affect the other. When measures such as these have been analyzed at all, they have usually been analyzed separately, even though the balance in the covariates of the various treatment groups achieved at baseline via the randomization process is often lost when interest is concentrated on the relapse behavior of relapsers alone. Far more informative—and less prone to hidden biases due to unbalanced unmeasured covariates—would be joint modeling of the two survival times, using random effects models that can induce correlation between successive survival times measured on the same individual. Although numerous models for inducing positive correlation have appeared in the last decade under the general heading of frailty modeling, for example, Yau (1997), they are limited by the fact that they force the within-subject correlation to be positive. Since the most heavily addicted people take longer to quit, but may also relapse faster, adequately handling these kinds of alcohol research problems will require extending the class of frailty models to accommodate negatively correlated survival times.

2.2.3. Methods Related to Formal Decision Theory. Many issues in treatment research have to do directly or indirectly with decision processes (individual or social) and utilities. To date, there has been little effort to apply the methods of formal decision analysis to problems in alcohol treatment. Alcohol treatment involves a complex decision (and gaming) process during extended periods of time. Such problems are typically studied under the heading of dynamic programming or gaming in the context of decision research (see, for example, Bell, Raiffa, & Tversky, 1988). Decision research on individual clinical decision-making could be used to develop dynamic clinical algorithms for managing classes of clients (Lindley, 1971). At a higher level in the treatment system, decision science methods could be used to formulate rational processes for managing groups of treatment providers to maximize systemwide benefits at minimum cost (managed care). In such instances, it is necessary to take into account utilities for complex outcomes (Keeney & Raiffa, 1976). The methods of formal decision analysis are well known and widely used in other contexts, but much work needs to be done to find the best adaptations of the well-known techniques to alcohol treatment problems.

2.2.4. Simulation and Nonlinear Modeling. There has been much mathematical research on complex dynamic systems in such fields as engineering, physics, and management. Even though alcoholics are complex dynamic systems (and themselves are embedded within complex dynamic systems), there have been relatively few attempts to use these system techniques in treatment research. One reason there have been few such attempts is, of course, that alcoholics are more complex than the simpler systems such as nuclear power plants for which simulation and nonlinear methods have been applied with some success. Nonetheless, there appears to be potential for applying these techniques, provided that adequately experienced researchers are involved in the modeling efforts.

There is some literature on the use of chaos theory and nonlinear dynamics in clinical work and research in psychology. Barton (1994) gives a summary introduction to the topics, and an edited volume by Masterpasqua and Perna (1997) covers a large range of topics in psychology. Tschacher (1996) applies analytical techniques from chaos theory to self-reports to examine the relationship between structure and function in the clinical setting.

There has been some work adapting these methods to alcohol research problems. Dean (1997) applied some insights from chaos theory to addictions research. Holder (1998) outlines the use of complex adaptive systems in developing computer models of alcohol policy and the outcomes of particular policy implementations. The Holder approach to model building attempts to integrate the best available research but extrapolates where necessary to form an integrated model for use by policy makers.

The National Institute of General Medical Sciences (1998) has described initiatives that focus on developing techniques for modeling complex biological systems through computer models and other techniques from complex systems

work. Alcohol researchers, too, must learn to take advantage of tools and ideas that have the potential to change the way we think about alcohol and its effects on individuals and society.

3. Final Remarks

As alcohol research continues to mature, it will follow the path that other fields have already traveled toward increasing integration of quantitative methods into research practice. Quantitative methods and thinking make possible innovations that are beyond the capacity of other approaches to emulate. At present, much effort is focused on taking advantage of statistics and technical mathematics to improve the rigor of our studies and the yield of scientific information from these studies. As the field progresses, however, there will be an increasing involvement of mathematics and computer modeling in the development of theory as well (Coombs, 1983). Alcohol researchers have a fundamental interest in supporting the rapid adaptation of advanced quantitative methods and ideas to foster the full development of our research capabilities.

References

- Allen, J.P., Litten, R.Z., Fertig, J.B., & Sillanaukee, P. (2000). Carbohydrate-deficient transferrin, γ -Glutamyltransferase, and macrocytic volume as biomarkers of alcohol problems in women. *Alcoholism: Clinical and Experimental Research* 24(4), 492–496.
- Allison, P.D. (1984). *Event History Analysis: Regression for Longitudinal Event Data*. Beverly Hills, CA: Sage.
- Babor, T.F., Longabaugh, R., Zweben, A., Fuller, R.K., Stout, R.L., Anton, R.F., et al. (1994). Issues in the definition and measurement of drinking outcomes in alcoholism treatment research. *Journal of Studies on Alcohol Supplement No. 12*, 101–111.
- Barton, S. 1994. Chaos, self-organization, and psychology. *American Psychologist* 49, 5–14.
- Bell, D., Raiffa, H., & Tversky, A. (1988). *Decision Making*. Cambridge, MA: Cambridge University Press.
- Bryk, A.S., & Raudenbush, S.W. (1992). *Hierarchical Linear Models*. Newbury Park, CA: Sage.
- Buscema, M. (1998). Theory: Foundations of artificial neural networks. *Substance Use and Misuse* 33, 17–199.
- Campbell, W.G. (1997). Is self-organized criticality relevant to alcoholism? *Journal of Addictive Diseases* 16, 41–50.
- Carbonari, J.P., Wirtz, P., Muenz, L., & Stout, R.L. (1994). Alternative analytical methods for detecting matching effects in treatment outcomes. *Journal of Studies on Alcohol Supplement No. 12*, 83–90.
- Choi, S.C. (1985). Monitoring clinical trials based on predictive probability of significance. *Biometrics* 45, 317–323.
- Cochran, W. (1983). *Planning and Analysis of Observational Studies*. New York: John Wiley and Sons.
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed. New York: Academic Press.
- Coombs, C. (1983). *Psychology and Mathematics: An Essay on Theory*. Ann Arbor: The University of Michigan Press.
- D'Agostino Jr., R.B. (1998). Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Statistics in Medicine* 17, 2265–2281.
- D'Agostino, R.B., & Rubin, D.B. (2000). Estimating and using propensity scores with partially missing data. *Journal of the American Statistical Association* 95(451), 749–759.

- Dean, A. (1997). *Chaos and Intoxication: Complexity and Adaptation in the Structure of Human Nature*. London: Routledge.
- Dehejai, R.H., & Wahba, S. (1999). Causal effects in nonexperimental studies: Reevaluating the evaluation of training programs. *Journal of the American Statistical Association* 94(448), 1053–1062.
- Diggle, P.J., Liang, K., & Zeger, S.L. (1994). *Analysis of Longitudinal Data*. New York: Oxford University Press.
- Geisser, S. (1993). *Predictive Inference: An Introduction*. London: Chapman & Hall.
- Harris, E.K., & Albert, A. (1991). *Survivorship Analysis for Clinical Studies*. New York: Marcel Dekker.
- Holder, H.D. (1998). Planning for alcohol-problem prevention through complex systems modeling: Results from SimCom. *Substance Use and Misuse* 33, 669–692.
- Holder, H., Cisler, R., Longabaugh, R., Stout, R., Treno, A., & Zweben, A. (2000). Alcoholism treatment and medical care costs from Project MATCH. *Addiction* 95(7), 1009–1023.
- Keeney, R., & Raiffa, H. (1976). *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*. New York: John Wiley and Sons.
- Lambert, D. (1992). Zero-inflated Poisson regression, with an application to defects in manufacturing. *Technometrics* 34, 1–14.
- Leon, A.C., Keller, M.B., Warshaw, M.G., Mueller, T.I., Solomon, D.A., Coryell, W., & Endicott, J. (1999). Prospective study of fluoxetine treatment and suicidal behavior in affectively ill subjects. *American Journal of Psychiatry* 156(2), 195–201.
- Liang, K.-Y., & Zeger, S.L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22.
- Lindley, D. (1971). *Making Decisions*, 2nd ed. New York: John Wiley and Sons.
- Little, R., & Rubin, D. (1987). *Statistical Analysis with Missing Data*. New York: John Wiley and Sons.
- MacCallum, R.C., & Austin, J.T. (2000). Applications of structural equation modeling in psychological research. *Annual Review of Psychology* 51, 201–226.
- Masterpasqua, F. & Perna, P. (eds.) (1997). *The Psychological Meaning of Chaos*. Washington, DC: American Psychological Association.
- Mullahy, J. (1986). Specification and testing of some modified count data models. *Journal of Econometrics* 33, 341–365.
- Muller, K.E., LaVange, L.M., Ramey, S.L., & Ramey, C.T. (1992). Power calculations for general linear multivariate models including repeated measures applications. *Journal of American Statistical Association* 87, 1209–1226.
- Musil, C.M., Jones, S.L., & Warner, C.D. (1998). Structural equation modeling and its relationship to multiple regression and factor analysis. *Research in Nursing and Health* 21, 271–281.
- National Institute on Alcohol Abuse and Alcoholism. (1994). *Twelve Step Facilitation Therapy Manual*. Washington, DC: U.S. Government Printing Office.
- National Institute on Alcohol Abuse and Alcoholism. (2001). *Project MATCH Hypotheses: Results and Causal Chain Analyses*. Washington, DC: U.S. Government Printing Office.
- National Institute of General Medical Sciences. (1998, February). *New approaches to the study of complex biological processes workshop report*.
- O'Malley, S., Jaffe, A., Chang, G., Schottenfeld, R.S., Meyer, R.E., & Rounsville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry* 49, 881–887.
- Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–29.
- Rosenbaum, P.R. (2001). Stability in the absence of treatment. *Journal of the American Statistical Association* 96(453), 210–219.
- Rubin, D.B., & Thomas, N. (2000). Combining propensity score matching with additional adjustments for prognostic covariates. *Journal of the American Statistical Association* 95(450), 573–585.
- Stout, R.L. (2000). What is a drinking episode? *Journal of Studies on Alcohol* 61(3), 455–461.
- Stout, R.L., Brown, P.J., Longabaugh, R., & Noel, N. (1996). Determinants of research follow-up participation in an alcohol treatment outcome trial. *Journal of Consulting and Clinical Psychology* 64(3), 614–618.

- Stout, R.L., Rubin, A., Zwick, W., Zywiak, W., & Bellino, L. (1999). Optimizing the cost-effectiveness of alcohol treatment: A rationale for extended case monitoring. *Addictive Behaviors* 24(1), 17–35.
- Stout, R.L., Wirtz, P., Carbonari, J.P., & Del Boca, F. (1994). Ensuring balanced distribution of prognostic factors in treatment outcome research. *Journal of Studies on Alcohol Supplement No. 12*, 70–75.
- Tschacher, W. (1996). The dynamics of psychosocial crises. *Journal of Nervous and Mental Disease* 184, 172–179.
- Wainer, H. (1986). *Drawing Inferences from Self-Selected Samples*. New York: Springer-Verlag.
- Wei, L.J. (1978). An application of an urn model to the design of sequential controlled trials. *Journal of the American Statistical Association* 73(363), 559–563.
- Wen, S.W., & Kramer, M.A. (1999). Uses of ecologic studies in the assessment of intended treatment effects. *Journal of Clinical Epidemiology* 52, 7–12.
- Yau, K.K.W. (1997). Use of generalised linear mixed models for the analysis of clustered survival data. *Biometrical Journal* 39, 3–11.
- Zeger, S.L., Liang, K.-Y., & Albert, P.S. (1988). Models for longitudinal data: A generalized estimating equation approach. *Biometrics* 44, 1049–1060.

Clinicians' Impact on the Quality of Substance Use Disorder Treatment

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Abstract. Clinicians' impact on substance use disorder treatment has been much less studied than therapy and patient variables. Yet, in this selective review of literature, a growing body of empirical work on clinicians' impact highlights several key issues that have relevance to both clinical practice and future research. These issues include clinicians' effect on treatment retention and outcome, professional characteristics, recovery status, adherence to protocols, countertransference, alliance, personality, beliefs about treatment, and professional practice issues. Specific recommendations are offered to help improve the quality of care that clinicians provide. In particular, it is suggested that greater accountability for clinicians' performance be balanced with increased support for their very difficult role. Methodological issues in studying clinicians are also addressed.

The vast majority of substance use disorder treatment programs (97 to 99%) provide some form of psychotherapy or counseling (London, 1990; Onken, 1991). Yet the clinicians who deliver this care have been little studied in research, in contrast to prevailing emphasis on types of treatments (e.g., CBT versus 12-step) and patient characteristics (Garfield, 1997; Imhof, Hirsch, & Terenzi, 1983; Miller, 1985; Najavits & Weiss, 1994; Onken & Blaine, 1990).

In this paper, our goal is to explore the impact of clinicians who deliver substance use disorder treatments. Through a selective review of empirical studies, we will highlight some major findings and discuss methodological

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issues for future research.¹ We review two broad categories of studies that involve clinicians, all of which were conducted within the substance use disorder field: those that evaluate clinicians' performance relative to each other and those that study clinician variables that may be relevant to the quality of their work (e.g., job satisfaction, beliefs about substance use disorder issues, therapeutic alliance, adherence).

Substance use disorder treatment may present particular challenges for clinicians beyond those inherent in mental health treatments in general. Patients with substance use disorder, it is believed, are more difficult to treat and more likely to evoke difficult countertransference than many other types of patients (Imhof, 1991; Imhof, Hirsch, & Terenzi, 1983; Najavits et al., 1995). Their case management needs may be enormous, with legal problems, homelessness, medical complications, financial issues, family problems, and HIV risk, many of which directly result from chronic substance use. High rates of dual diagnoses (Regier et al., 1990) and dropout (Craig, 1985; Crits-Christoph & Siqueland, 1996; McCaul & Svikis, 1991) can also intensify treatment difficulties (Weiss & Najavits, 1998).

Moreover, substance use disorder treatment is characterized by a variety of unique professional practice issues. It is the only disorder whose treatment during this past century has been primarily outside of mainstream mental health, via Alcoholics Anonymous and other nonprofessional self-help groups (Najavits & Weiss, 1994; Strug, Priyadarsini, & Hyman, 1986). It is the only disorder in which a major psychosocial intervention aside from psychotherapy (12-step groups) remains the dominant treatment model, and the only one whose system of care remains largely separate (in training, funding, certification, and even separate branches within the National Institutes of Health). It is the only disorder in which treatment is provided primarily by either counselors or 12-step groups, rather than the advanced-degree specialists typical of mental health (social work, psychology, psychiatry). It is also the only disorder in which clinicians' experience of the disorder themselves (recovery status) is openly acknowledged and promoted as a positive attribute. Finally, it is unique in being both a serious psychiatric disorder (substance dependence) yet also a socially valued and accepted activity when used in small amounts without obvious problems (Keller, 1986). As a result of such cultural and historical characteristics, philosophical and practical differences tend to emerge on various topics. For example, is psychopharmacology an appropriate treatment for substance use disorder? Is harm reduction an acceptable goal when 12-step groups adhere to an abstinence model? Is substance use disorder a lifelong disease? The tendency of clinicians to rely on ideology rather than research data appears to be a notable issue at this point (Miller & Hester, 1995; Roche et al., 1995).

As will be seen in the review of studies below, clinicians vary greatly. Clinicians are not the monolithic "constant" previously assumed in most

¹ Our search was limited to English-language studies of adult psychosocial treatments, focusing on psychoactive substance use disorders.

treatment research (Crits-Christoph, Beebe, & Connolly, 1990; Kiesler, 1966). Improved understanding of the power they hold and their professional experiences, can, we believe, lead to increased support for their role and ultimately increase their capacity to help patients under their care.

1. Clinicians' Impact on Substance Use Disorder Treatment Retention and Outcome

One of the most important findings from several decades of research on substance use disorder treatment is that *clinicians are a key factor influencing treatment outcome and retention*. This finding has emerged repeatedly in a variety of studies (Najavits & Weiss, 1994; Project MATCH Research Group, under review), although, paradoxically, this result was rarely the intent of the studies. It is a finding that has been called "surprising" (Milmoe et al., 1967) and "serendipitous" (Miller, Taylor, & West, 1980, p. 600). Yet to most frontline clinicians, program administrators, and patients, this result would seem obvious; it is widely known that some practitioners are highly regarded and others are avoided. Research, however, is only beginning to catch up to this known clinical phenomenon. Part of the reason for this disparity is that most outcome studies are designed to evaluate treatments but not clinicians. They compare, for example, cognitive therapy with drug counseling but do not evaluate each clinician conducting these treatments (i.e., how does clinician #1 compare to clinician #2?). Ironically, however, clinicians typically account for *more* variance in patient outcomes than do differences between active treatments or patient baseline characteristics, a result which holds both in the substance use disorder field and psychotherapy research in general (Crits-Christoph, 1991; Luborsky et al., 1986, 1997; Najavits & Weiss, 1994; Project MATCH Research Group, under review).

Tables 1 and 2 provide examples of key substance use disorder studies that have evaluated clinicians' differences in two measures of effectiveness: patient outcomes, that is, symptomatic improvement from pre- to posttreatment (Table 1) and retention, that is, how long patients stay in treatment (Table 2).

The studies mirror the general finding in the psychotherapy literature (Garfield, 1997; Luborsky et al., 1997; Najavits & Strupp, 1994) that clinicians vary greatly. Each of the studies (except the NIDA Collaborative Cocaine Treatment Study, Crits-Christoph et al., 1997, and the study by Gottheil, Sterling, Weinstein, & Kurtz, 1994) found significant clinician effects. Moreover, the studies span a wide diversity of patient populations (inpatient, outpatient), primary substances (alcohol, cocaine, opiates), research designs (e.g., naturalistic versus controlled trials), presence or absence of manualized treatments, and types of practitioners (e.g., counselors, therapists). When interpreting such studies, however, conclusions can only be tentative at this point, given how few studies actually test for clinician differences and the methodological limitations of most of the studies listed (e.g., nonrandom assignment of patients to clinicians, retrospective design,

Table 1. Clinicians' Impact on Retention in Substance Use Disorder Treatment: Examples of Key Studies

Study	Therapist Sample	Type of Treatment	Patient Sample	Measures	Key Findings
Raynes & Patch (1971)	8 psychiatric residents	Inpatient psychiatric treatment (no manuals) ^b	Various, but including patients with substance use disorder	AMA/AWOL ^a rates from inpatient treatment during 1 year	Psychiatric residents' rates of AMA/AWOL patients ranged from 0–40%.
Rosenberg et al. (1976)	16 alcohol counselors	Alcohol counseling (no manuals) ^b	Alcoholics	Patients' attendance rate during 18 weeks of treatment	Counselors' average attendance rates of patients' ranged from 27 to 67%, and were significantly different as early as 9 weeks into treatment.
Kleinman et al. (1990)	7 therapists	Outpatient supportive-expressive, family therapy (using manuals), and group therapy (without manual)	Cocaine-dependent patients	Patients' attendance during 24 sessions	The strongest predictor of patient drop out was therapist assignment. For example, the best therapist retained 81% of patients for 4+ sessions; the worst retained only 14%.
Craig (1985) ^b	Staff on a substance use disorder treatment unit during 6 years	Inpatient, general substance use disorder treatment (no manuals) ^b	Substance use disorders	AMA rates	The AMA rate was reduced from 70 to 20% during 6 years by implementing staff training, increasing staff presence, group incentive, and cash bonuses.
Gottheil et al. (1994)	8 intake clinicians	Outpatient substance use disorder intake (no manual) ^c	Cocaine-dependent patients	Return rate after intake visit	No difference in patient return rate based on intake clinician assignment, clinician academic training, gender, or race.
McCaul & Svikis (1991)	7 clinicians	Outpatient substance use disorder (no manual)	Substance use disorders ^d	Successful discharge rates and treatment retention	Rates for successful discharges ranged from 17–54% per clinician; rates for early drop out ranged from 14–61%.

^a AMA = "against medical advice"; AWOL = "absent without leave."

^b This study does not provide comparison of clinicians to each other, but it is included because it addresses retention in substance abuse treatment.

^c Assumed because no mention of manual.

^d Assumed, but not specified in article.

Table 2. Clinicians' Impact on *Outcomes* in Substance Use Disorder Treatment: Examples of key studies

Study	Therapist Sample	Type of Treatment	Patient Sample	Outcome	Key Findings
Miller et al. (1980)	9 para-professional therapists	Three types of short-term behavioral treatment (using manuals)	Alcoholics	Patients' drinking at 7 months	The least effective therapist had a 25% rate of successful patient outcomes; the most effective had a 100% rate. Moreover, therapists' degree of empathy accounted for 67% of variance in patient outcomes.
Luborsky et al. (1985)	9 clinicians	Cognitive supportive-expressive, or drug counseling (using manuals)	Opiate addicts receiving methadone	7 outcome measures	Significant differences among clinicians on each of the 7 outcome measures, with average effect size ranging from .13 (least effective) to .74 (most effective).
McLellan et al. (1988)	4 counselors	Drug counseling (no manuals) ^a	Opiate-dependent patients receiving methadone	5 outcome measures	"Marked and consistent differences among the counselors." Counselor differences shown on four of the five outcome measures.
Project MATCH (under review)	80 clinicians	12-step facilitation, cognitive-behavioral, motivational enhancement therapy (using manuals)	Alcoholics	Percent days abstinent and drinks per drinking days	Therapist effects were found for each condition, ranging from 8-12% of the outcome variance (with a pattern of findings that varied based on type of site, i.e., outpatient versus aftercare, and timing, i.e., during versus after treatment). No clinician differences in retention of patients.
Crits-Christoph et al. (1997)	40 clinicians	Cognitive, supportive-expressive, or drug counseling (using manuals)	Cocaine-dependent	Overall drug use; cocaine use	No significant therapist effects on either outcome measure.
Luborsky et al. (1997)	27 clinicians (combined across 3 studies)	Cognitive, supportive-expressive, or drug counseling (using manuals)	VA sample of opiate-dependent patients receiving methadone	5 outcome measures during 6 months of treatment	Therapists differed significantly (e.g., one clinician had a mean caseload change of 82% on the ASI ^b psychiatric subscale, and another had -1%).

^a This study does not provide comparison of clinicians to each other, but it is included because it addresses retention in substance abuse treatment.

^b Addiction Severity Index (McLellan et al., 1992).

small clinician samples, uncontrolled numbers of patients assigned to clinicians (Crits-Christoph & Mintz, 1991; Najavits & Weiss, 1994).

Some of the studies evaluated whether clinician differences "disappear" when patient baseline characteristics are taken into account. A common belief is that clinician differences are largely attributable to patients' characteristics (such as severity, functioning level, etc.). Yet, in studies that evaluated this question, patient baseline differences did *not* account for the results found (Luborsky et al., 1997; Najavits & Weiss, 1994, Project MATCH Research Group, under review). For example, in Project MATCH, clinician differences emerged even when controlling for patients' drinking severity and readiness for change at intake.

2. Clinicians' Professional Background Characteristics

Clinicians' professional background characteristics, such as years of experience, training, etc., might be presumed to influence effectiveness. Yet every major review of the literature during the past several decades has concluded that, overall, such clinician professional characteristics do not predict their effectiveness in substance use disorder research and psychotherapy research more generally (Christensen & Jacobson, 1994; Najavits & Weiss, 1994 for a thorough review of the literature on professional versus paraprofessional clinicians see Christensen & Jacobson, 1994). In Project MATCH, this also held true except for one finding (i.e., 12-step clinicians' training and years of experience were negatively associated with patients' drinking outcomes) (Project MATCH Research Group, under review). A counterargument can be made that improved methodology might lead to a stronger association between therapist professional background characteristics and outcomes (Snyder, 1997), but thus far, results have been highly consistent, even though they fly in the face of "clinical wisdom."

Rather than examining clinicians' background characteristics, it is likely to be more productive to examine aspects of clinicians' actual performance on the job (Luborsky et al., 1997). In an interesting study by McLellan et al. (1988), for example, clinicians who appeared the most organized and thorough in their professional record keeping, enforcement of clinic rules, and use of treatment resources had the best outcomes with opiate-dependent patients.

3. Matching Patients to Clinicians

Some studies have evaluated whether treatment quality can be improved by matching patients to clinicians on the basis of a variety of characteristics (e.g., gender, race). Matching studies typically follow the predominant model of matching patients to *treatments* rather than to clinicians (Gastfriend & McLellan, 1997), but some studies have addressed the latter (albeit mostly

matching on easy-to-measure variables such as race, gender, training, etc.). As one example of such work, Sterling et al. (1998) studied 967 African-American cocaine-dependent outpatients but found no relationship between any of five clinician variables (including race, gender, and training) and treatment retention, which echoed an earlier study by the same team that found no relationship of these variables to outcomes in a sample of 634 cocaine-dependent patients (Gottheil, Thornton, & Weinstein, 1997). Overall, the studies reviewed in Sterling et al. (1998) have largely found null or mixed results for clinician–patient matching.

4. Clinicians' Recovery Status

Of particular relevance to the substance use disorder field, clinicians in recovery (i.e., those who had a substance use disorder problem) versus those not in recovery also show no significant differences in effectiveness despite more than 50 studies on this topic, according to McLellan et al. (1988). In Project MATCH, this also held true (Project MATCH Research Group, under review). This lack of difference contrasts with clinical lore, which typically asserts that being in recovery translates into better ability to help patients.

5. Adherence and Competence

The advent of manualized treatments—whose goal is to improve the quality of treatment by standardizing it in written form—has led to the development of clinician adherence scales (Addis, 1997; Luborksy & DeRubeis, 1984). Such scales are designed to evaluate whether clinicians are conducting specific treatments within the parameters of the treatment manual and usually include ratings of both adherence (how closely the clinician followed the manual) and competence (the quality with which they conducted the work). Such scales also allow testing discriminability (whether a clinician's conduct of a treatment can be differentiated from another treatment) (Addis, 1997; Luborksy & DeRubeis, 1984). Of course, process–outcome relationships may be more complex than linear cause–effect associations. More complex associations, where therapist behaviors are influenced by patient states, need to be taken into account in relating these variables to outcome (Stiles, Honos-Webb, & Surko, 1998).

Several large-scale substance use disorder treatment trials (Project MATCH and the NIDA Collaborative Cocaine Treatment Study), as well as some smaller studies, have produced adherence scales for a variety of substance use disorder treatments. Currently, psychometric data appear quite strong for adherence scales for cognitive therapy, drug counseling, supportive-expressive therapy, motivational enhancement therapy, family therapy, and dynamic cognitive therapy (Barber et al., 1996, 1997; Carroll et al., 1998; Hogue et al., 1998). Such scales can be used in clinical practice, as well as in research studies, to improve treatment quality.

Perhaps the most relevant finding to date is that clinicians' effects on outcomes lessen when adherence to treatment increases, according to a major meta-analysis (which included but was not limited to substance use disorder outcome studies) (Crits-Christoph, 1991). This may mean that if manualized treatments become the norm in clinical settings, the wide variation in clinicians' skills may be reduced. In the study by Luborsky et al. (1985), outcome was associated with clinicians' "purity" of techniques (i.e., the degree to which clinicians conformed to a treatment manual and only to that treatment manual). Purity was related to better outcomes across all clinicians in the study and within clinician caseloads, highlighting the important connection between the clinician and the treatment techniques used.

A study by Broome et al. (1996) addressed "counselor competence" (but not adherence per se) based on patients' rating of their clinicians on four items ("well-organized," "self-confident," "helpful," and "knowledgeable"). Competence showed both high internal consistency (.81) and a strong relationship to rearrest rates of 279 patients with substance use disorder on probation, accounting for 42% of variance, one of the highest predictors in their model, even when patients' prior arrest record was taken into account.

6. Clinicians' Emotional Responses (Countertransference)

An area strongly emphasized in clinical writing is clinicians' emotional responses to patients (Imhof, 1991; Imhof, Hirsch, & Terenzi, 1983; Najavits et al., 1995), with the presumption that patients with substance use disorder may effect heightened countertransference because they are typically perceived as more difficult than other patients. Moreover, the "ideal clinician" for patients with substance use disorder is often described in terms of particular emotions, such as a high degree of charisma, optimism, and enjoyment working with substance use disorder patients, and a low degree of cynicism, blame, boredom, hostility, and control (Flores, 1988; Gustafson, 1991; Imhof, Hirsch, & Terenzi, 1983; Miller, 1985; Vannicelli, 1989; Washton & Stone-Washton, 1990; Woody et al., 1990; Zweben, 1989).

Two studies illustrate empirical work in this area. One study (Milmoe et al., 1967) determined, based on audiotape ratings, that the more anger and anxiety in doctors' voices during an initial interview, the less likely patients were to follow through on alcoholism treatment. Another study, using data from the NIDA Collaborative Cocaine Treatment Study (Najavits et al., 1995), found that clinicians who treated cocaine-dependent patients became more negative during the course of 6 months of treatment despite initially positive views of their patients. That study also found four factors in clinicians' emotional responses, in descending order: "therapist in conflict with self," "therapist focused on own needs," "positive connection," and "therapist in conflict with the patient." Finally, 12-step counselors had more positive views of their patients than cognitive or supportive-expressive therapists. Relating such findings to treatment outcomes will be a logical next step for research.

7. Clinicians' Interpersonal Functioning/Therapeutic Alliance

The clinician characteristic most associated with clinicians' effects in substance use disorder treatment has been in-session interpersonal functioning (broadly, the ability to build a positive relationship with patients) (Najavits & Weiss, 1994). In the alcoholism study by Miller et al. (1980), "accurate empathy" on the Truax Scale (rated by clinicians' colleagues) accounted for 67% of the clinicians' outcome results; clinicians' experience level was not related to either empathy or outcome. In one of the more rigorous studies on this topic, Valle (1981) found a strong positive association between the interpersonal functioning of eight alcohol counselors and their patients' abstinence from drinking 6 to 24 months after treatment. Interpersonal functioning referred to "empathy, genuineness, respect, and concreteness" based on counselors' written responses to stimulus statements (a method previously validated). Valle observed that the counselors ranged widely in interpersonal functioning, reinforcing the finding discussed previously that clinicians may vary considerably in performance. This study was notable for its large sample size (247 patients) and random assignment of patients to counselors.

A study by Miller, Benefield, and Tonigan (1993) is particularly instructive for the substance use disorder field. They compared a supportive therapist style with a confrontational therapist style in the treatment of alcoholics. They found that the more clinicians confronted patients, the more patients drank (with a strong correlation of .65 for drinking outcomes at one year). The use of confrontation as a style particular to substance use disorder treatment thus deserves particular reevaluation.

One of the most prolific areas of work in this domain has been assessment of the therapeutic alliance between patients and clinicians, mirroring the general psychotherapy literature which has found that alliance is one of the most robust predictors of treatment outcome (Bergin & Garfield, 1994). It is included here because it is widely believed that clinicians contribute to the alliance (although it is not exclusively a clinician variable because, as a dyadic variable, it involves patients as well). Results within the substance use disorder field have been somewhat mixed. A few studies have found clear associations between clinicians' ratings of alliance and effectiveness (Bell, Montoya, & Atkinson, 1997; Connors et al., 1997; Najavits et al., 1998). For example, in Project MATCH, Connors et al. (1997) found that both clinician and patient ratings of the alliance were strong predictors of alcoholic outpatients' treatment participation and drinking behavior during treatment and 12-month follow-up, even after controlling for a variety of other sources of variance. Luborsky et al. (1985) found that the development of a "helping alliance" was correlated with outcome. In a dual diagnosis sample of women with PTSD, Najavits et al. (1998) found a positive association between therapists' ratings of alliance and patients' retention in treatment. A dual diagnosis study of schizophrenics found the odd result that a more positive alliance (as rated by patients) was associated with lower participation in aftercare (Westreich, Rosenthal, & Muran, 1996).

A number of studies have not found an association between alliance and outcomes, however. Belding et al. (1997), studying opiate-dependent patients in methadone treatment, initially noted that 3-month alliance measures (especially counselors' ratings) predicted reductions in drug use, as measured by weekly urinalysis results and 6-month self-report data. However, controlling for urinalysis results in the previous month rendered insignificant the correlations between 3-month alliance and subsequent drug use; moreover, the alliance was unrelated to treatment retention or improvement in psychiatric symptomatology. Oejehagen et al. (1997), studying alcoholics randomized to either multimodal behavioral therapy or psychodynamic therapy, found no relationship between alliance and drinking outcomes for either therapy, although alliance was associated with mood outcomes at 6 months for the behavioral therapy condition. Barber et al. (1999), studying 252 cocaine-dependent patients treated with psychotherapy or drug counseling, found that patients' report of the alliance predicted outcome on drug related measures at the 1-month assessment, but not at the 6-month assessment. Alliance also predicted improvement in depressive symptoms at 6-months. In short, it is too early to draw firm conclusions, but it appears that counselors' interpersonal functioning is an important predictor of quality substance use disorder treatment. When studying the association between clinician and patient alliance, results are sometimes strong, but sometimes not. Given the mixed findings thus far, this is an area ripe for future research.

8. Clinicians' Personality Characteristics

Several studies have attempted to study clinicians' personality characteristics. A few results have been found, but it is difficult to draw any consistent conclusions, because there are few studies and they vary greatly in the personality variables evaluated.

Better treatment retention has been found associated with clinicians' introversion on the Eysenck Personality Inventory (Rosenberg et al., 1976); field dependence (Dahl, 1981) and higher need for nurturance but less need for aggression, achievement, and abasement (Schorer, 1965) (the latter two studies are summarized in a paper by the Project MATCH Research Group; Project MATCH Research Group, under review).

Treatment outcomes have been studied as well. In Project MATCH (Project MATCH Research Group, under review), 29 personality scales were administered to the 54 therapists in three different theoretical orientations. Relating personality characteristics to patient outcome (percent days abstinent), there were a few findings, particularly for 12-step clinicians, although all correlations are relatively low (ranging from .21 to .37). Better outcome was associated with 12-step clinicians who had higher need for aggression and lower masculinity and femininity; lower needs for achievement, nurturance, deference; and a lower conceptual level. For motivational enhancement therapy, better outcomes

were associated with lower need for aggression, lower masculinity, and higher need for nurturance. For cognitive-behavioral clinicians, no personality characteristics predicted outcomes. Snowden and Cotler (1974) studied 25 recovering counselors on the staff of an urban drug counseling center in relation to patients' outcomes: missed medications, random urine screen results, and treatment attendance. They found, oddly, that the best counselors were more hypochondriacal, paranoid, manic, and were lower in ego strength. Thrower and Tyler (1986) studied the counseling staff at five addiction treatment centers, who were all recovering paraprofessionals. Peers and supervisors of the counselors provided effectiveness ratings. Therapists rated as more effective, on the Edwards Personal Preference Schedule were more "dominant," more "heterosexual," less "deferential," and lower on "order."

9. Clinicians' Beliefs about Substance Use Disorder Treatment

One of the most potentially promising areas of work is the study of clinicians' views on substance use disorder topics, such as the value of 12-step groups, acceptability of a harm reduction model, endorsement of a disease model of addiction, the relevance of DSM-IV diagnoses, what interventions are helpful or harmful for recovery, and what causes addictions problems to begin with (e.g., genetics, psychological problems, etc.) (Caetano, 1988; Ogborne et al., 1998; Polcin, 1997). A number of studies surveyed clinicians; however, these are rarely if ever related to "hard" empirical results (such as outcome, treatment retention, referral patterns, etc.). One study that attempted to do so was that of Kang and colleagues (Kang, Magura, Nwakeze, & Demsky, 1997), who surveyed 112 counselors in methadone maintenance clinics on a variety of issues relevant to addictions treatment. They found that counselors differed in their attitudes on many issues; however, they did not find any association between attitudes and counseling process variables (e.g., percentage of patients testing positive for cocaine or heroin during the week; number of patients seen; or referrals to other services). Thus, whether counselor beliefs actually influence behavior (Azjen & Fishbein, 1980) remains a topic for future research. As Ogborne et al. (1998) concluded, this area of work is in its infancy.

Some findings in this area are worth mentioning because they highlight topics that are directly related to treatment quality. For example, Hshieh and Srebalus (1997) surveyed 119 psychologists and 110 addictions counselors about alcoholism and how it might be treated. They found the two professional groups very similar in referral use, accepting a disease analogy for alcoholism, positive views of a 12-step model of recovery, and strong spiritual and/or religious beliefs. However, psychologists were more willing to accept controlled drinking as an alternative goal to abstinence, whereas addictions counselors reported more personal experience with problem drinking. A study by Ogborne et al. (1998) of frontline addictions staff found that they strongly supported cognitive-behavioral treatments but viewed pharmacological treatments

as detrimental. In Project MATCH, 12-step clinicians endorsed a disease model of alcoholism significantly more and a psychosocial model significantly less than CBT and MET clinicians (Project MATCH Research Group, under review). Such results may have important implications for developing staff training, educating staff about outcome research, and openly discussing philosophies of treatment.

A frequent survey topic has been clinicians' views of 12-step groups, likely because such groups are both a unique aspect of substance use disorder treatment and they adhere to several assumptions quite different from those of traditional psychotherapy (e.g., overt spirituality, addiction as a lifelong disease, and emphasis on peer-led rather than professionally led groups). Thus far, the literature appears to show less controversy than might be expected: most surveys we found had very positive views of 12-step groups, an absence of ideological conflict between mental health and 12-step philosophies, and a strong willingness to refer patients to self-help groups (Freimuth, 1996; Hsieh & Srebalus, 1997; Humphreys, 1997; Osborn, 1997; Roche et al., 1995; Wheeler & Turner, 1997).

There is little research focused on beliefs about interventions other than the 12-step or disease model at this point (Ogborne et al., 1998), but this area is likely to grow with the recent burst of empirical research on psychosocial treatments other than 12-step (e.g., MET, CBT, psychodynamic) (Crits-Christoph et al., 1997; Project MATCH Research Group, 1997).

Another branch of work is studying clinicians' views of their own competence in treating patients with substance use disorder, which may have direct implications for the selection, training, and supervision of staff. One of the earliest studies of this sort was Hayman in 1956 (cited in Galanter, 1993), who found that 90% of psychiatrists reported that they were unable to successfully treat alcoholism (Najavits & Weiss, 1994). A more recent study of 94 counselors (Wheeler & Turner, 1997) found that generic counselors did not tend to feel competent working with clients who have alcohol problems; feelings of competence increased with greater experience working with alcoholics and, to a lesser extent, with more hours of specialist training.

Finally, another area is the study of clinical judgment, that is, how accurate clinicians are in their judgments about clinical topics. Arising from cognitive psychology, this, too, is an area largely undeveloped thus far in substance use disorder treatment. One example of an interesting study in this is that of Breslin et al. (1997). They asked eight clinicians treating 212 outpatient problem drinkers to predict "How confident are you that the participant will make positive changes in his/her drug or alcohol abuse problems?", scaled 0–100. They found that clinicians' prognostic ratings contributed significantly to the prediction of outcome (days abstinent and drinks per day at 6-month follow-up) over and above the predictive power of various patient pretreatment variables as predictors. This result disappeared, however, when in-treatment drinking data were included in the model. They concluded that clinicians' judgment may be useful in situations when in-treatment drinking data are not available.

10. Professional Practice Issues

Given the notable challenges inherent in substance use disorder treatment, there are a variety of professional practice issues that warrant attention when considering clinicians' quality of service delivery.

One often-noted phenomenon is a high rate of burnout (Gustafson, 1991; Elman & Dowd, 1997). As Gustafson said, the central message to clinicians is "Do more, and do it better." He reviews a variety of professional practice issues that make substance use disorder treatment difficult for clinicians and systems: "unacceptably low" salaries and fringe benefits, location of drug treatment programs in less desirable areas, the often poor physical work environment of drug programs, high staff turnover, and a shortage of job candidates with relevant qualifications. A recent survey of job satisfaction among 231 addictions counselors found that 76% reported that they would leave their jobs within the next 5 years. They were least satisfied with their opportunities for advancement and most satisfied with the opportunity to be of help to others (Evans & Hohenshil, 1997).

A major strain on clinicians' ability to provide adequate care is systems issues. For example, the lack of integration between mental health and substance use disorder treatment systems can make clinicians' jobs difficult when trying to coordinate dual diagnosis care (Weiss & Najavits, 1998). Accessing substance use disorder care is also known as a problem. For example, a recent survey of 54 primary therapists in a public managed care psychiatric setting (Uttaro et al., 1998) asked them to rate their difficulty in providing or arranging adequate services in 19 areas. The area ranked second (after housing) was substance use disorder services, and the most common problem cited was a lack of availability of services. When considering that many patients with substance use disorder seek treatment in systems that are not designed for them, such as primary care and many mental health settings, the need for greater attention to such issues is paramount.

The issue of "impaired professionals" (i.e., those who have a substance use disorder) is a serious concern, no matter who the professional is treating, but becomes perhaps even more problematic when treating substance use disorder populations. Unfortunately, according to research on ethics complaints to professional boards, for both psychiatrists and addictions counselors, impairment due to substance use disorder is very high on the list of ethics complaints against them (Lasalandra, 1995; St. Germaine, 1997). Another common complaint for both groups is having a sexual relationship with a client (Lasalandra, 1995; St. Germaine, 1997). Yet, it is believed that ethical training is minimal (St. Germaine, 1997).

11. Clinician-Targeted Interventions

One of the most creative attempts to address clinicians' quality of services has been to target clinicians themselves with interventions to improve outcomes.

As McCaul and Svikis (1991) note, clinicians are routinely rewarded in a non-contingent fashion through incentives such as salary, outside training, comp and flex time, and access to resources such as clerical services and funds to purchase educational materials. These authors list a variety of clinician-targeted interventions and preliminary pilot data on them. For example, they monitored clinicians' ($n = 6$) success with patients for 4 months without intervention (using specific standards such as number of sessions), then implemented monthly written feedback on the performance of each client in their caseload. They found a significant increase in clinicians' performance postintervention, noting that "the success of this program is striking given the minimal nature of the goal-setting and feedback intervention." Another recent innovation is allowing consumers access to information on clinicians' professional background and any formal ethics complaints against them (e.g., in Massachusetts where this is now available for all medical doctors, including psychiatrists, from the Massachusetts Medical Society). Presumably, such information may help increase clinicians' performance through a system of "market forces."

One notable study that relates to the issue of developing clinician-focused interventions is by Zanis et al. (1997). In the context of comparing three data collection methods for quantifying and categorizing treatment services provided in a methadone program (one of which was a counselor service interview), they found that (1) counseling sessions rarely focused on specific problem domains, (2) counselors and patients disagreed about the quality of treatment services, and (3) counselors "rounded-up" time spent counseling. These findings might suggest that greater attention to providing counselors with appropriate guidelines in these domains and monitoring them in some ongoing way could be helpful.

12. Clinician Selection and Training

It is widely believed that one of the best ways to improve the quality of clinicians' service delivery is attention to clinician selection and training. Yet there are very few studies that empirically evaluate these issues in the substance use disorder field, in part because they can be difficult studies to conduct. In fact, only one study to date has examined the effects of manual-based psychotherapy/counseling training for the treatment of substance use disorders.

As part of the NIDA Cocaine Collaborative Study, Crits-Christoph et al. (1998) describe the effects of training on the skill levels of 65 therapists who delivered manual-guided therapies to 202 cocaine-dependent patients. Three treatment modalities were studied: supportive-expressive therapy, cognitive therapy, and individual drug counseling. Therapists for the supportive-expressive and cognitive therapy conditions were primarily doctoral level clinicians; the drug counseling approach was taught to bachelor's- and master's-level clinicians. Clinicians, each of whom treated four training cases, were evaluated in terms of their improvements in competence in learning one of these modalities. The

effects of manual-guided training on the therapeutic alliance were also examined through a hierarchical linear modeling approach that assessed changes both within cases (over sessions) and across the four training cases. A large effect across cases was found for training in cognitive therapy. Supportive-expressive therapists and individual drug counselors demonstrated learning trends over sessions, but not over training cases. It was found that training in supportive-expressive and cognitive therapy did not have a negative impact on the therapeutic alliance, although alliance scores for trainees in drug counseling initially decreased slightly but then rebounded to initial levels.

Despite the relatively large numbers of patients and clinicians involved in this study, several limitations of the research should be noted. In particular, clinicians in all three modalities were highly experienced when training began (approximately 10 years of postdegree clinical practice). Training may have more of an impact on relatively inexperienced clinicians; more experienced clinicians are either already highly competent or resistant to changing their methods. It should also be noted that the scales used to assess clinician competence are relatively crude and may be insensitive to change. Clearly, substantially more research is needed on the topic of training and dissemination of manual-based treatment methods to clinicians.

13. Methodological Issues in Studying Clinicians

We wish to highlight two important methodological issues relevant to the impact of clinicians on the outcome of treatment for substance use disorders, although both issues apply to studies of other disorders as well. First, studies of clinician background, personality, or work skills need to employ the clinician as the unit of analysis. Most studies of clinician characteristics are post hoc exploratory analyses from studies that were designed with the patient as the unit of analysis (e.g., randomized clinical trials of treatment approaches). Although surveys of clinicians' attitudes (e.g., Hsieh & Srebalus, 1997) have often used a large number of clinicians, a relatively small number of clinicians is typically used in outcome studies, thereby drastically limiting statistical power for examining the impact of the clinician. It is possible that the clinician has a substantially greater role in affecting retention and outcome than the studies reviewed in this article have indicated, but this remains to be detected through designs with adequate statistical power.

The second issue pertains to the impact of the clinician with regard to the design of studies examining treatment modalities. Despite repeated discussion of this issue (Crits-Christoph, Beebe, & Connolly, 1990; Crits-Christoph & Mintz, 1991; Martindale, 1978), investigators often fail to examine clinician differences in studies of treatment modalities or fail to recognize the implication of clinician differences for understanding the generalizability of treatment effects.

Simply put, if clinician differences in outcome (retention or process variables) exist, such variability needs to be accounted for in understanding the

extent to which potential treatment differences generalize to other similarly selected and trained clinicians. This can be accomplished by including the clinician as a random factor in statistical models examining treatment effects. Only if clinician differences are emphatically nonsignificant (as examined in preliminary analyses), should the clinician factor be ignored in the analysis of treatment effects.

Fortunately, evidence exists suggesting that attempts to standardize the delivery of treatment (e.g., through the use of treatment manuals) tends to minimize the size of clinician differences in outcomes (Crits-Christoph et al., 1991). However, if clinician differences are found, as is often the case, the inclusion of the clinician as a factor in the analysis of treatment effects will generally limit statistical power considerably (since the number of clinicians becomes the degrees of freedom for assessing treatment effects), severely hindering an investigator's ability to understand the generalizability of treatment effects. At the least, we recommend that investigators routinely examine whether clinician differences exist and discuss any effects in the context of findings regarding clinician differences.

Summary and Discussion

In this article, we attempted to highlight empirical work focusing on clinicians' contribution to the quality of substance use disorder treatment (or lack thereof). Based on the studies reviewed, we believe that there is enormous potential to improve the quality of substance use disorder treatment by paying greater attention to clinician effects, in both treatment settings and research studies. Suggestions include the following.

The need to select and evaluate clinicians based on their "track record." Available evidence thus far suggests that clinicians' actual record of work with patients (e.g., retention and outcome within their caseload) varies greatly among clinicians. Moreover, past assumptions about particular levels of training, experience, or other simple therapist variables do not account for such differences. Selecting and evaluating clinicians based on how they actually perform, using standardized measures, is rarely done but is an effort that could greatly improve the quality of care as well as future research. It is striking that for decades there has been a call for greater attention to clinician differences, yet neglect of this topic remains the norm (Crits-Christoph, Beebe, & Connolly, 1990; Kiesler, 1966; Leukefeld, Pickens, & Schuster, 1991; Luborsky et al., 1986; Najavits & Weiss, 1994; Project MATCH Research Group, under review; Valle, 1981).

Providing more support to clinicians can improve clinical care. Many systems issues prevent clinicians from doing their best. Problems of burnout, job dissatisfaction, continued splits between mental health and substance use disorder treatment systems, low salaries and poor work environments (particularly for substance use disorder counselors), and lack of ongoing training once on the job make it very difficult for clinicians to do the work they are hired to do. Concrete efforts to provide more peer and supervisory support on the job, offer

training for difficult areas of substance use disorder treatment (e.g., dual diagnosis, HIV risk behaviors), increase salaries, provide career advancement tracks within substance use disorder treatment, and other assistance can improve clinicians' work, and as a result, ultimately filter down to patients (Gustafson, 1991; Schulman-Marcus, 1986). Taking a respectful and validating stance toward clinicians on the front lines is key, while simultaneously (as per point 1) also monitoring and "weeding out" poor performers.

Improving dissemination of empirically based knowledge. The need to move our empirical knowledge base into actual clinical practice ("technology transfer") remains a serious challenge (Polcin, 1997; Shanley, Lodge, & Mattick, 1996). Helping clinicians learn and implement the diverse and growing number of empirically based protocols for substance use disorder treatment is one important effort. Deconstructing enduring "myths" that persist in the field is another example of such dissemination (e.g., despite consistent evidence to the contrary for several decades, many clinicians believe that being in recovery makes one a better clinician; that higher credentials result in better treatment; that 12-step groups are the only treatment that works for substance use disorder; or that all psychopharmacology for substance use disorders represents another form of "addiction").

Broadening the assessment of clinician variables. The easiest clinician variables to measure are, unfortunately, some of the least relevant to the quality of service delivery (e.g., gender, race, age, training, years of experience). Variables with much more relevance to quality care include empathy, ability to establish an alliance, emotional reactions to patients, professional demeanor and record keeping, ability to enforce clinic rules and make appropriate referrals to further care, beliefs about substance use disorder topics, etc. Greater attention to these variables in relation to outcomes could be powerful.

Viewing clinicians as a key to improved treatment. Historically, there has been a great deal of emphasis on patient and treatment factors that impact the quality of care, but much more rarely has there been attention to the clinicians who deliver those treatments to patients (and interactions between treatments, patients, and clinicians). This blind spot has begun to be addressed in some of the studies reviewed in this paper, yet remains quite pervasive in the field overall. (Indeed, if it came from a patient, this tendency, which flies in the face of substantial research and clinical evidence, is likely to be interpreted as pathological "resistance"!). Testing for clinician effects in all outcome studies (Crits-Christoph, Beebe, & Connolly, 1990), describing clinicians in as much detail as possible (Najavits & Weiss, 1994), having them fill out a battery of measures before beginning employment and/or participating in research, attempting to identify "outlier" clinicians (Project MATCH Research Group, under review), and generally taking the stance that clinicians have the power to impact outcomes (Craig, 1985) are all ways to help improve this deficit.

How good is good enough? It is easy to create a list of saintly attributes that all clinicians should possess, but empirical identification of minimum standards for quality care has not yet occurred. What expectable retention in treatment or

outcomes can we expect of clinicians? Can certification standards for substance use disorder counselors (and other professionals) be linked to empirical standards (Schulman-Marcus, 1986; Valle, 1981)? What are reasonable criteria for firing someone due to poor quality work? In research studies, initial criteria for selecting therapists often still relate to therapists' professional background characteristics (Carroll et al., 1994), rather than objective measures of interpersonal functioning or other qualities that may be more related to later performance.

Education for clinicians outside of the substance use disorder field. It has repeatedly been noted that many clinicians fail to assess, recognize, or adapt treatment to patients with substance disorder (see the review by Polcin, 1997). Historically, also, the mental health field has had low interest in substance use disorder treatment, and mental health and substance use disorder systems are still widely perceived as difficult to integrate. Many patients with substance use disorder receive inadequate care (Polcin, 1997). Taking a broad view to provide education to clinicians in other settings (e.g., primary care, mental health) might markedly improve care and/or help route patients to treatments designed for them.

Education for consumers of care. Providing information to consumers of substance use disorder treatment (e.g., patients with substance use disorder and their families) can be another avenue to improve quality. For example, patients can be taught about topics such as how to evaluate the quality of care they receive, when to stay versus leave treatment if it feels that it is not working, and what is inappropriate behavior (e.g., clinicians' sexual abuse of patients).

Targeting clinicians for interventions. There is a wide range of empirically studied treatments for patients with substance use disorder but very little implementation of interventions to improve clinicians' performance [e.g., pay based on performance, clear criteria for what constitutes good quality work, formalized supervisory feedback (McCaul & Svikis, 1991), use of adherence ratings in clinical practice]. Such efforts might have the danger of alienating clinicians due to fears of being monitored, distrust of empirical measurement, or other concerns. However, they could also provide a very direct way to improve the quality of care, if implemented carefully and with sensitivity.

As Carkhuff and Berenson concluded several decades ago, counseling, like all human relationships, can be "for better or worse" (Valle, 1981). Clinicians do impact substance use disorder treatment to a marked degree. Their work is enormously difficult, and they often succeed in helping people despite systems problems, treatment challenges, and often inadequate support for their role. As this selective review illustrates, however, there are some excellent empirical attempts to address clinicians' impact on treatment, which hopefully will see expansion as a clinical and research topic in years ahead.

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References

- Addis, M.E. (1997). Evaluating the treatment manual as a means of disseminating empirically validated psychotherapies. *Clinical Psychology Science and Practice* 4, 1-11.
- Azjen, I., & Fishbein, M. (1980). *Understanding Attitudes and Predicting Social Behavior*. Englewood Cliffs, NJ: Prentice-Hall.
- Barber, J.P., Krakauer, I., Calvo, N., Badgio, P.C., et al. (1997). Measuring adherence and competence of dynamic therapists in the treatment of cocaine dependence. *Journal of Psychotherapy Practice and Research* 6, 12-24.
- Barber, J.P., Luborsky, L., Crits-Christoph, P., Thase, M.E., Weiss, R.D., Frank, A., Onken, L., & Gallop, R. (1999). Therapeutic alliance as a predictor of outcome in treatment of cocaine dependence. *Psychotherapy Research* 9, 54-73.
- Barber, J.P., Mercer, D., Krakauer, I., & Calvo, N. (1996). Development of an adherence/competence rating scale for individual drug counseling. *Drug and Alcohol Dependence* 43, 125-132.
- Belding, M.A., Iguchi, M.Y., Morral, A.R., & McLellan, A.T. (1997). Assessing the helping alliance and its impact in the treatment of opiate dependence. *Drug and Alcohol Dependence* 48, 51-59.
- Bell, D.C., Montoya, I.D., & Atkinson, J.S. (1997). Therapeutic connection and client progress in drug abuse treatment. *Journal of Clinical Psychology* 53, 215-224.
- Bergin, A.E., & Garfield, S.L. (eds.). (1994). *Handbook of Psychotherapy and Behavior Change* (4th ed.) New York: John Wiley.
- Breslin, F.C., Sobell, M.B., Sobell, L.C., Buchan, G., & Cunningham, J.A. (1997). Toward a stepped care approach to treating problem drinkers: The predictive utility of within-treatment variables and therapist prognostic ratings. *Addiction* 92, 1479-1489.
- Broome, K.M., Knight, K., Hiller, M.L., & Simpson, D.D. (1996). Drug treatment process Indicators for probationers and prediction of recidivism. *Journal of Substance Abuse Treatment* 13, 487-491.
- Caetano, R. (1988). Concepts of alcohol dependence: The two worlds of research and treatment. *Alcohol and Alcoholism* 23, 225-227.
- Carroll, K.M., Connors, G.J., Cooney, N.L., Diclemente, C.C., Donovan, D.M., Kadden, R.R., Longabaugh, R.L., Rounsville, B.J., Wirtz, P.W., & Zweben, A. (1998). Internal validity of Project MATCH treatments: Discriminability and integrity. *Journal of Consulting and Clinical Psychology* 66, 290-303.
- Carroll, K.M., Kadden, R.M., Donovan, D.M., Zweben, A., & Rounsville, B.J. (1994). Implementing treatment and protecting the validity of the independent variable in treatment matching studies. *Journal of Studies on Alcohol Supplement No.* 12, 149-155.
- Christensen, A., & Jacobson, N.S. (1994). Who (or what) can do psychotherapy: The status and challenge of nonprofessional therapies. *Psychological Science* 5, 8-14.
- Connors, G.J., Carroll, K.M., Diclemente, C.C., Longabaugh, R., & Donovan, D.M. (1997). The therapeutic alliance and its relationship to alcoholism treatment participation and outcome. *Journal of Consulting and Clinical Psychology* 65, 588-598.
- Craig, R.J. (1985). Reducing the treatment drop out rate in drug abuse programs. *Journal of Substance Abuse Treatment* 2, 209-219.
- Crits-Christoph, P. (1991). Meta-analysis of therapist effects in psychotherapy outcome studies. *Psychotherapy Research* 1(2), 81-91.
- Crits-Christoph, P., Baranackie, K., Kurcias, J., Beck, A.T., et al. (1991). Meta-analysis of therapist effects in psychotherapy outcome studies. *Psychotherapy Research* 1, 81-91.
- Crits-Christoph, P., Beebe, K., & Connolly, M. (1990). Therapist effects in the treatment of drug dependence: Implications for conducting comparative treatment studies. *NIDA Research Monograph* 104, 39-49.
- Crits-Christoph, P., & Mintz, J. (1991). Implications of therapist effects for the design and analysis of comparative studies of psychotherapies. *Journal of Consulting and Clinical Psychology* 59, 20-26.
- Crits-Christoph, P., & Siqueland, L. (1996). Psychosocial treatment for drug abuse: A selected review and recommendations for national health care. *Archives of General Psychiatry* 53, 749-756.

- Crits-Christoph, P., Siqueland, L., Blaine, J., Frank, A., Luborsky, L., Onken, L.S., Muenz, L., Thase, M.E., Weiss, R.D., Gastfriend, D.R., Woody, G., Barber, J.P., Butler, S.F., Daley, D., Bishop, S., Najavits, L.M., Lis, J., Mercer, D., Grffin, M.L., Beck, A., & Moras, K. (1997). The NIDA Cocaine Collaborative Treatment Study: Rationale and methods. *Archives of General Psychiatry* 54, 721–726.
- Dahl, M.E. (1981). Matching patients and therapists on field dependence-independence, A-B therapist style, and the Navran scale to cut down on dropouts from therapy among alcoholics. *Dissertation Abstracts International* 41, 3884-B.
- Elman, B.D., & Dowd, E.T. (1997). Correlates of burnout in inpatient substance abuse treatment therapists. *Journal of Addictions and Offender Counseling* 17, 56–65.
- Evans, W.N., & Hohenshil, T.H. (1997). Job satisfaction of substance abuse counselors. *Alcoholism Treatment Quarterly* 15, 1–13.
- Flores, P. (1988). *Group Psychotherapy with Addicted Populations*. New York: Haworth.
- Freimuth, M. (1996). Psychotherapists' beliefs about the benefits of 12-step groups. *Alcoholism Treatment Quarterly* 14, 95–102.
- Galanter, M. (1993). *Network Therapy for Alcohol and Drug Abuse: A New Approach in Practice*. New York: Basic Books.
- Garfield, S.L. (1997). The therapist as a neglected variable in psychotherapy research. *Clinical Psychology: Science and Practice* 4, 40–89.
- Gastfriend, D.R., & Mclellan, A.T. (1997). Treatment matching: Theoretic basis and practical implications. *Medical Clinics of North America* 81, 1–22.
- Gottheil, E., Sterling, R.C., Weinstein, S.P., & Kurtz, J.W. (1994). Therapist/patient matching and early treatment dropout. *Journal of Addictive Diseases* 13, 169–176.
- Gottheil, E., Thornton, C.C., & Weinstein, S.P. (1997). Treatment structure, client coping methods, and response to brief individual counseling: Preliminary findings in a substance dependent sample. *Journal of Addictive Diseases* 16, 51–65.
- Gustafson, J. (1991). Do more... and do it better: Staff-related issues in the drug treatment field that affect the quality and effectiveness of services. *NIDA Research Monograph* 106, 53–62.
- Hogue, A., Liddle, H.A., Rowe, C., Turner, R.M., Dakof, G.A., & Lapann, K. (1998). Treatment adherence and differentiation in individual versus family therapy for adolescent substance abuse. *Journal of Counseling Psychology* 45, 104–114.
- Hshieh, S.Y., & Srebalus, D.J. (1997). Alcohol treatment issues: Professional differences. *Alcoholism Treatment Quarterly* 15, 63–73.
- Humphreys, K. (1997). Clinicians' referral and matching of substance abuse patients to self-help groups after treatment. *Psychiatric Services* 48, 1445–1449.
- Imhof, J. (1991). Countertransference issues in alcoholism and drug addiction. *Psychiatric Annals* 21, 292–306.
- Imhof, J., Hirsch, R., & Terenzi, R. (1983). Countertransferrential and attitudinal considerations in the treatment of drug abuse and addiction. *International Journal of Addiction* 18, 491–510.
- Kang, S.Y., Magura, S., Nwakeze, P., & Demsky, S. (1997). Counselor attitudes in methadone maintenance. *J Maint Addict* 1, 41–58.
- Keller, M. (1986). The old and the new in the treatment of alcoholism. In D.L. Strug, S. Priyadarsini, M.M. Hyman (eds.), *Alcohol Interventions: Historical and Sociocultural Approaches*. New York: Haworth Press.
- Kiesler, D. (1966). Some myths of psychotherapy research and the search for a paradigm. *Psychological Bulletin* 65, 110–136.
- Kleinman, P., Woody, G., Todd, T., et al. (1990). Crack and cocaine abusers in outpatient psychotherapy. *National Institute on Drug Abuse Research Monograph* 104, 24–38.
- Lasalandra, M. (1995, June 5). Sexual trouble stalks Mass. shrinks. *Boston Herald* 1, 20–21.
- Leukefeld, C.G., Pickens, R.W., & Schuster, C.R. (1991). Improving drug abuse treatment: Recommendations for research and practice. *NIDA Research Monograph* 394–406.
- London, P. (1990). Research priorities for psychotherapy and counseling in the treatment of drug abuse: The psychotherapy research perspective. *NIDA Research Monograph* 104, 121–127.

- Luborsky, L., Crits-Christoph, P., McLellan, A.T., Woody, G., Piper, W., Liberman, B., Imber, S., & Pukonis, P. (1986). Do therapists vary much in their success? Findings from four outcome studies. *American Journal of Orthopsychiatry* 56, 501–512.
- Luborsky, L., McLellan, A.T., Diguer, L., Woody, G., & Seligman, D.A. (1997). The psychotherapist matters: Comparison of outcomes across twenty-two therapists and seven patient samples. *Clinical Psychology: Science and Practice* 4, 53–65.
- Luborsky, L., McLellan, A.T., Woody, G., & O'Brien, C. (1985). Therapist success and its determinants. *Archives of General Psychiatry* 42, 602–611.
- Luborsky, L., & Derubeis, R.J. (1984). The use of psychotherapy treatment manuals: A small revolution in psychotherapy research style. *Clinical Psychology Review* 4, 5–14.
- Martindale, C. (1978). The therapist-as-fixed-effect fallacy in psychotherapy research. *Journal of Consulting and Clinical Psychology* 46, 1526–1530.
- McCaull, M., & Svikis, D. (1991). Improving client compliance in outpatient treatment: Counselor-targeted interventions. *NIDA Research Monograph* 106, 204–217.
- McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argeriou, M. (1992). The fifth edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment* 9, 199–213.
- McLellan, A.T., Woody, G.E., Luborsky, L., & Goehl, L. (1988). Is the counselor an "active Ingredient" in substance abuse rehabilitation? An examination of treatment success among four counselors. *Journal of Nervous and Mental Disease* 176, 423–430.
- Miller, W. (1985). Motivation for treatment: A review with special emphasis on alcoholism. *Psychological Bulletin* 98, 84–107.
- Miller, W., Taylor, C., & West, J. (1980). Focused versus broad-spectrum behavior therapy for problem drinkers. *Journal of Consulting and Clinical Psychology* 48, 590–601.
- Miller, W.R., Benefield, R.G., & Tonigan, J.S. (1993). Enhancing motivation for change in problem drinking: A controlled comparison of two therapist styles. *Journal of Consulting and Clinical Psychology* 61, 455–461.
- Miller, W.R., & Hester, R.K. (1995). Treatment for alcohol problems: Toward an informed eclecticism. In R.K. Hester & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*. Boston: Allyn & Bacon.
- Milmoe, S., Rosenthal, R., Blane, H., et al. (1967). The doctor's voice: Postdictor of successful referral of alcoholic patients. *Journal of Abnormal Psychology* 72, 78–84.
- Najavits, L.M., Griffin, M.L., Luborsky, L., Frank, A., Weiss, R.D., Liese, B.S., Thompson, H., Nakayama, E., Siqueland, L., Daley, D., & Onken, L.S. (1995). Therapists' emotional reactions to substance abusers: A new questionnaire and initial findings. *Psychotherapy* 32, 669–677.
- Najavits, L.M., & Strupp, H.H. (1994). Differences in the effectiveness of psychodynamic therapists: A process-outcome study. *Psychotherapy* 31, 114–123.
- Najavits, L.M., & Weiss, R.D. (1994). Variations in therapist effectiveness in the treatment of patients with substance use disorders: An empirical review. *Addiction* 89, 679–688.
- Najavits, L.M., & Weiss, R.D. (1994). The role of psychotherapy in the treatment of substance use disorders. *Harvard Review of Psychiatry* 2, 84–96.
- Najavits, L.M., Weiss, R.D., Shaw, S.R., & Muenz, L.R. (1998). "Seeking safety": Outcome of a new cognitive-behavioral psychotherapy for women with posttraumatic stress disorder and substance dependence. *Journal of Traumatic Stress* 11, 437–456.
- Oejehagen, A., Berglund, M., & Hansson, L. (1997). The relationship between helping alliance and outcome in outpatient treatment of alcoholics: A comparative study of psychiatric treatment and multimodal behavioural therapy. *Alcohol and Alcoholism* 32, 241–249.
- Ogborne, A.C., Wild, T.C., Braun, K., & Newton-Taylor, B. (1998). Measuring treatment process beliefs among staff of specialized addiction treatment services. *Journal of Substance Abuse Treatment* 15, 301–312.
- Onken, L. (1991). Using psychotherapy effectively in drug abuse treatment. *NIDA Research Monograph* 106, 267–278.
- Onken, L.S., & Blaine, J.D. (1990). Psychotherapy and counseling research in drug abuse treatment: Questions, problems, solutions. *NIDA Research Monograph* 104, 1–8.

- Osborn, C.J. (1997). Does disease matter? Incorporating solution-focused brief therapy in alcoholism treatment. *Journal of Alcohol and Drug Education* 43, 18–30.
- Polcin, D.L. (1997). The etiology and diagnosis of alcohol dependence: Differences in the professional literature. *Psychotherapy* 34, 297–306.
- Project Match Research Group (under review). Therapist effects in three treatments for alcohol problems.
- Project Match Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–29.
- Raynes, A.E., & Patch, V.D. (1971). Distinguishing features of patients who discharge themselves from psychiatric wards. *Comprehensive Psychiatry* 12, 473–479.
- Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., & Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 264, 2511–2518.
- Roche, A.M., Parle, M.D., Stubbs, J.M., Hall, W., et al. (1995). Management and treatment efficacy of drug and alcohol problems: What do doctors believe? *Addiction* 90, 1357–1366.
- Rosenberg, C., Gerrein, J., Manohar, V., et al. (1976). Evaluation of training in alcoholism counselors. *Journal of Studies on Alcohol* 37, 1236–1246.
- Schorer, C.G. (1965). Defiance and healing. *Comprehensive Psychiatry* 6, 184–190.
- Schulman-Marcus, F. (1986). *Counselor Credentialing—Exploration of the Issues*. New York: Narcotic and Drug Research.
- Shanley, C., Lodge, M., & Mattick, R.P. (1996). Dissemination of research findings to alcohol and other drug practitioners. *Drug and Alcohol Review* 15, 89–94.
- Snowden, L., & Cotler, S. (1974). The effectiveness of paraprofessional ex-addict counselors in a methadone treatment program. *Psychotherapy: Theory, Research and Practice* 4, 331–338.
- Snyder, D.K. (ed.) (1997). Do therapists matter? *Clinician's Research Digest* 15, 4.
- St. Germaine, J. (1997). Ethical practices of certified addiction counselors: A national survey of state certification boards. *Alcoholism Treatment Quarterly* 15, 63–72.
- Sterling, R.C., Gottheil, E., Weinstein, S.P., & Serota, R. (1998). Therapist/patient race and sex matching: Treatment retention and 9-month follow-up outcome. *Addiction* 93, 1043–1050.
- Stiles, W.B., Honos-Webb, L., & Surko, M. (1998). Responsiveness in psychotherapy. *Clinical Psychology: Science and Practice* 5, 439–458.
- Strug, D.L., Priyadarsini, S., & Hyman, M.M. (1986). *Alcohol Interventions: Historical and Sociocultural Approaches*. New York: Haworth Press.
- Thrower, J., & Tyler, J. (1986). Edwards personal preference schedule correlates of addiction counselor effectiveness. *International Journal of Addiction* 21, 191–193.
- Uttaro, T., Vali, F., Horwitz, A.V., & Henri, W.F. (1998). Primary therapists' views of managed care. *Psychological Reports* 82, 459–464.
- Valle, S. (1981). Interpersonal functioning of alcoholism counselors and treatment outcome. *Journal of Studies on Alcohol* 42, 783–790.
- Vannicelli, M. (1989). *Group Psychotherapy with Adult Children of Alcoholics: Treatment Techniques and Countertransference Considerations*. New York: Guilford.
- Washton, A., & Stone-Washton, N. (1990). Abstinence and relapse in cocaine addicts. *Journal of Psychoactive Drugs* 22, 135–147.
- Weiss, R.D., & Najavits, L.M. (1998). Overview of treatment modalities for dual diagnosis patients: Pharmacotherapy, psychotherapy, and 12-step programs. In H.R. Kranzler & B.J. Rounsvaile (eds.), *Dual Diagnosis and Treatment: Substance Abuse and Comorbid Medical and Psychiatric Disorders*. New York: Marcel Dekker.
- Westreich, L.M., Rosenthal, R.N., & Muran, J.C. (1996). A preliminary study of therapeutic alliance and dually diagnosed inpatients. *American Journal on Addictions* 5, 81–86.
- Wheeler, S., & Turner, L. (1997). Counselling problem drinkers: The realm of specialists, Alcoholics Anonymous or generic counsellors? *British Journal of Guidance and Counselling* 25, 313–326.

- Woody, G.E., McLellan, A.T., Luborsky, L., & O'Brien, C.P. (1990). Psychotherapy and counseling for methadone-maintained opiate addicts: Results of research studies. *NIDA Research Monograph 104*, 9–23.
- Zanis, D.A., McLellan, A.T., Belding, M.A., & Moyer, G. (1997). A comparison of three methods of measuring the type and quantity of services provided during substance abuse treatment. *Drug and Alcohol Dependence 49*, 25–32.
- Zweben, J.E. (1989). Recovery-oriented psychotherapy: Patient resistances and therapist dilemmas. *Journal of Substance Abuse Treatment 6*, 123–132.

Natural Resolution of Alcohol-Related Problems

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Psychotherapy research has numerous instances where yesterday's nuisance variable became today's substantive research question (Tucker, 1999). Recall, for example, how the "dodo bird verdict" on the equivalence of psychotherapy outcomes (Luborsky, Singer, & Luborsky, 1975) led to relabeling "nonspecific factors" as "common factors" that were worthy of study as determinants of outcomes and how this transition set the stage for the later development of the influential transtheoretical model of change (e.g., Prochaska, DiClemente, & Norcross, 1992). This same transition is now occurring with respect to the natural resolution of alcohol problems and other addictive behaviors in the absence of interventions. Previously termed spontaneous remission, following from Eysenck's (1952) seminal psychotherapy outcome study, the natural resolution process has long been viewed as a nuisance variable that requires statistical control in outcome evaluations. Until recently, comparing change in the presence versus absence of treatment was considered a basic requirement of methodologically adequate evaluations, and natural resolution was relegated to being an element of a necessary control condition, rather than an object of study in its own right.

Another impediment to the study of natural resolution is specific to the alcohol field and reflects the continuing influence of the disease model on American views of drinking problems and their resolution (Peele, 1993; Roizen & Fillmore, 2001). The presumably progressive and irreversible nature of alcohol problems is incompatible with the possibility that affected individuals could change their behavior without the benefit of intensive and extended treatment or involvement in Alcoholics Anonymous (AA). To the extent that

natural resolution was acknowledged, it typically was trivialized by assertions that it occurred only among problem drinkers with less serious problems. Note that similar arguments were used during the controlled drinking controversy to dismiss findings of moderation drinking by former problem drinkers.

What has transpired to move natural resolution into a more central position in the alcohol research field? First are the documented limitations of treatment in promoting behavior change and the mounting evidence that some problem drinkers resolve their problem without interventions (Sobell, Cunningham, & Sobell, 1996; Tucker & King, 1999). Studying naturally occurring change thus may help to improve interventions. Second is a growing appreciation that, in the aggregate, improvements in outcomes are likely to come from more widespread dissemination of interventions over the population in need, rather than from further refinements in clinical treatments—that is, by shifting from a clinical to a public health perspective on service delivery (Humphreys & Tucker, 2002; Institute of Medicine, 1990). Natural resolution research may advance understanding of barriers to service use and help devise interventions that have lower thresholds and are more appealing to the underserved majority of problem drinkers who do not use professional treatments. Third are cost-effectiveness considerations in today's managed care environment that are driving health care in the direction of using the least intensive and least expensive intervention first and then "stepping up" the level of care only when necessary (Sobell & Sobell, 1999). Scarce intensive treatment resources should not be misapplied to problem drinkers who can benefit from less intensive and less costly interventions. Fourth, research using untreated samples offers an opportunity to study the conditions that influence problem development, maintenance, resolution, and relapse in the absence of confounding effects due to treatment experiences and may aid the development and refinement of theories of alcohol use and abuse (Tucker & King, 1999).

1. State of Knowledge

Smart's (1975/76) review of natural resolution was the first of many reviews during the past 25 years (e.g., Blomqvist, 1996; Fillmore, 1988; Klingemann, Sobell, Barker et al., 2001; Mariezcurrera, 1994; Roizen, Cahalan, & Shanks, 1977; Sobell, Ellinstad, & Sobell, 2000; Sobell, Sobell, & Toneatto, 1992; Stall & Biernacki, 1986; Tucker & King, 1999; Walters, 2000; Watson & Sher, 1998). Several well known early studies (e.g., Robins, Helzer, & Davis, 1975; Tuchfeld, 1980; Schachter, 1982) documented the phenomenon with addictive behaviors and promoted interest in it. About 60% of the relevant research has been published since 1990 (Sobell et al., 2000). As summarized next, most research falls into one of two categories: (1) surveys that assessed the incidence and prevalence of natural resolution, often in relation to treatment-assisted resolutions, using large population samples; or (2) smaller studies that used

community-based convenience samples and investigated more intensively the circumstances and processes associated with natural resolution. This body of work is necessarily correlational. The natural resolution process is insufficiently understood to conduct experiments that manipulate variables thought to promote it.

1.1. Epidemiology of Treatment-Assisted and Natural Resolutions

Six robust findings from survey research have defined this area of inquiry:

- (1) Seeking help for drinking problems is uncommon. Surveys (e.g., Grant, 1996; Narrow, Regier, Rae, Manderscheid, & Locke, 1993; Regier, Narrow, Rae, Manderscheid, Locke, & Goodwin, 1993; Sobell et al., 1996) have consistently shown that less than 25% of the population in need seek help from professional providers or from the voluntary sector (e.g., AA) (reviewed by Marlatt, Tucker, Donovan, & Vuchinich, 1997; Schmidt & Weisner, 1999). For example, the 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES) yielded a 1-year population prevalence rate of 7.4% for any alcohol use disorder (abuse or dependence diagnosed using DSM IV criteria; American Psychiatric Association, 1994), but only 9.9% of persons so diagnosed had received alcohol treatment during the past year. When problem drinkers do seek help, their care is diffused throughout the professional and voluntary sectors, and only a minority receive specialized substance abuse services (Narrow et al., 1993). They also tend to overuse medical services compared to persons without drinking problems, but not to an extent that exceeds use by patients with other serious chronic health conditions (e.g., diabetes) (Fortney, Booth, & Curran, 1999).
- (2) Most problem drinkers who resolve their problems do so without interventions. Although resolution rates vary across studies, depending on definitions and measures of problem drinking and resolution (Roizen et al., 1977; Room, 1977), natural resolution is the dominant pathway for positive change (the same is true for smoking resolutions). For example, two representative surveys of adult Canadians who had resolved a drinking problem for at least 12 months indicated that about 75% had done so without treatment (Sobell et al., 1996). The remainder had used an alcohol-related service, mutual-help groups, or counseling.
- (3) Abstinent and moderation drinking outcomes are proportionately higher in treated and untreated samples, respectively. For example, using data from the NLAES survey, Dawson (1996) found that sustained abstinence during the past year was about twice as likely among treated (38.8%) than untreated (16.4%) problem drinkers who met DSM IV criteria for alcohol dependence. The reverse was true for moderation outcomes (28.0% and 57.8% of treated and untreated drinkers, respectively). This common finding (e.g., Armor & Meshkoff, 1983;

- Sobell et al., 1996) suggests that treatment may facilitate abstinent outcomes without necessarily increasing total positive outcomes, if both abstinence and moderation are considered successes.
- (4) Treatment-seeking samples tend to have more serious problems than natural resolution samples, but natural resolutions occur even among individuals with alcohol dependence. Part of the reason moderation outcomes are more common among natural resolution samples is that drinkers with more serious problems are overrepresented in treatment-seeking samples (Grant, 1996; Marlatt et al., 1997). Nevertheless, natural resolution samples have significant problems, and they usually include some individuals with moderate to substantial alcohol dependence (e.g., Armor & Meshkoff, 1983; Dawson, 1996; Humphreys & Weisner, 1999; Sobell et al., 1992; Tucker, Vuchinich, & Rippens, 2002a,b). When differences are found, they usually involve more serious psychosocial and health problems due to drinking in treatment-seeking than in natural resolution samples (Marlatt et al., 1997).
 - (5) Resolution patterns show variation over the life span. Surveys had repeatedly shown that substance use is highest in adolescence and early adulthood and then declines with age (e.g., Hilton, 1987; Fillmore, 1988; Williams & DeBakey, 1992). Many persons with problems resolve them by midlife without interventions. Age-related patterns of resolution differ somewhat as a function of gender (Fillmore, 1988). Resolution among men is most frequent in youth and old age and, although less well studied, resolution among women is most frequent after their problems peak during the 40s. Whether these life-span changes reflect a maturation process, the effects of adult role transitions, or are a function of the duration of problem drinking (independent of age of onset) is difficult to explicate because these dimensions tend to be naturally confounded and most studies have not controlled for cohort and period effects (Levenson, Aldwin, & Spiro, 1998).
 - (6) The resolution process is influenced by the surrounding environmental context and by individuals' personal resources. Robins and colleagues' (e.g., Robins et al., 1975; Robins, 1993) landmark prospective survey of soldiers who abused heroin in Vietnam showed very high natural resolution rates when they returned stateside. The study directed attention to the natural resolution phenomenon and to the role of the environment and drug access in problem development and resolution. Subsequent studies (discussed later) have continued to show that extra-treatment, environmental variables exert powerful effects on both natural and treatment-assisted resolutions, thus indicating that the Robins study was not an anomaly of the Vietnam experience (reviewed by Tucker, Vuchinich, & Gladsjo, 1990/91; Tucker & King, 1999).

1.1.1. Summary. Surveys have revealed the occurrence and extent of natural resolutions and the related problem of insufficient help-seeking by persons in

need. Both issues have been overshadowed by research on treatment seekers, who tend to have more serious problems and are a minority of persons with problems. Surveys are not well suited, however, to revealing the contexts and processes associated with resolution attempts made with and without interventions. As summarized next, these questions are better addressed in smaller studies that assess environment–behavior relations through time.

1.2. Environmental Contexts Surrounding Natural Resolutions

The life circumstances that surround natural resolution have been a long-standing research focus. Typically, former problem drinkers who maintained stable abstinence for several years have been solicited from the community and asked to report retrospectively on the circumstances that existed when they initiated their resolution. Contrary to the assertion by some critics (e.g., Watson & Sher, 1998), retrospective designs using former problem drinkers with stable resolutions have been an appropriate starting point because of the recurring nature of drinking problems. This is an efficient research strategy until natural resolution is sufficiently understood to support the selection of problem drinkers who are likely to resolve without treatment for inclusion in prospective research. A few recent prospective studies (e.g., Humphreys, Moos, & Finney, 1995; Tucker et al., 2002a) have yielded results similar to well-conducted retrospective studies, which increases confidence in this body of research.

The quality of research has improved during the past decade, in part because of the adoption of methodological practices that are standard in treatment research, such as the use of procedures known to enhance the accuracy of verbal reports (e.g., structured interviews, recall aids, collateral interviews). Another key improvement has been the inclusion of a control group of active problem drinkers to ascertain which variables and processes are uniquely associated with natural resolution, rather than with problem drinking generally (Sobell et al., 1992). Select studies have included other improvements: (1) lengthening the assessment interval to cover a several year period that surrounds the onset of resolution, which allows for the study of both initiating and maintaining conditions (e.g., Klingman, 1991; Tucker, Vuchinich, & Gladsjö, 1994); (2) including groups of former problem drinkers who have maintained stable abstinence or moderation drinking (e.g., King & Tucker, 1998, 2000; Sobell et al., 1992); and (3) determining the extent to which a core set of contextual changes is associated with natural and intervention-assisted resolutions and the unique contribution interventions may have in promoting change (e.g., Humphreys et al., 1995; Tucker, Vuchinich, & Pukish, 1995; Tucker et al., 2002b). These are the four major findings from this line of work:

- (1) Stable resolutions typically are associated with increased negative events before resolution that decrease after quitting or moderating drinking and with increased positive events during the first year or so of maintenance. The negative events usually occur in areas of functioning that are

impaired by drinking (e.g., family and social relations; health, work, or legal problems). The positive events usually reflect improved social relations and health habits (e.g., better diet, more exercise, quitting smoking). These contextual changes, it has been found, are uniquely associated with resolution in studies that included a control group of untreated, active problem drinkers and assessed events in their lives during comparable intervals (e.g., King & Tucker, 1998; Tucker et al., 1994; Tucker et al., 2002a). The pattern has also been observed in natural resolutions of other addictive behaviors, including drug abuse (Klingemann, 1991), obesity (Tinker & Tucker, 1997), bulimia (Crawford & Tucker, 2001), and gambling (Hodgins & El-Quebaly, 2000). Although the correlational research designs preclude firm causal inferences, the contextual changes are consistent with negative events serving a motivational function and positive events serving a reinforcing function in the change process. Of the two sets of contextual changes, increased positive events during maintenance have been more reliably observed, including in prospective studies (Humphreys et al., 1995; Tucker et al., 2002a).

- (2) Interventions often function to consolidate prior reductions in abusive drinking practices and to support continued improvement during maintenance. Studies that examined the temporal relation of help-seeking episodes to the onset of significant reductions in drinking found that many problem drinkers abstained or quit drinking abusively on their own, several days or weeks before they sought help (e.g., Blomqvist, 1996; Maisto, Sobell, Sobell, Lei, & Sykora, 1988; Tucker, 1995). This suggests that extratherapeutic forces are often sufficient to motivate initial change but that maintenance may require, or be facilitated by, participation in interventions. Humphreys et al. (1995), for example, observed that previously untreated, lower income problem drinkers who initiated abstinence on their own relied heavily on AA during maintenance. Other studies of resolutions achieved by problem drinkers who did and did not participate in AA or treatment (Blomqvist, 1996; Tucker et al., 1996; Tucker et al., 2002b) found that interventions enhanced positive events and improved functioning during maintenance, beyond the positive changes associated with natural resolution alone.
- (3) Drinking pathways to natural resolution are variable. Common resolution patterns include (1) abruptly initiated, continuous abstinence; (2) initial abstinence followed by resumption of moderate drinking; or (3) gradual reductions in problem drinking followed by stable moderate drinking (King & Tucker, 2000; Sobell et al., 1992; Tucker et al., 2002a). Variable pathways to moderation have also been noted in studies of treatment samples (e.g., Miller & Page, 1991). The evidence is mixed, however, regarding the relation between preresolution drinking patterns and the likelihood of achieving moderation, and it seems

to vary with help-seeking status. Treatment studies suggest that moderation is more likely among persons with continuous, near daily drinking patterns (reviewed by Rosenberg, 1993), whereas natural resolution studies suggest that moderation is more likely among persons with more variable drinking patterns (Dawson, 1996; King & Tucker, 2000). The issue merits more study.

- (4) Problem drinkers who resolved without assistance generally recognized that they had alcohol-related problems but had concerns about helping resources that deterred use. Many substance abusers find available interventions stigmatizing, unappealing, and ill suited to addressing their problems (reviewed by Marlatt et al., 1997). Such views are especially acute among those who resolved their problems on their own (e.g., Cunningham, Sobell, Sobell, Agrawal, & Toneatto, 1993). These problem drinkers typically had recognized their drinking problem years ago, usually after the onset of near daily heavy drinking, but did not regard their problem as serious enough to seek help from treatment or AA. These kinds of concerns were more influential in decisions not to seek help compared to convenience issues or economic barriers to use.

1.2.1. Summary. Achieving stable resolution is often a lengthy process and may involve one of several pathways to abstinence or moderation. Natural and treatment-assisted resolutions are surrounded by contextual changes that seem important for motivating and maintaining change. Interventions appear to be sought out and make positive contributions to the change process, primarily during the maintenance phase. However, many problem drinkers, and especially those who achieve natural resolutions, find available interventions unappealing.

2. Gaps in Knowledge and Research Opportunities

2.1. *Investigating Natural Resolution across the Distribution of Problem Drinkers*

The full range of problem drinkers who resolve naturally, as identified in population surveys, needs to be studied in the more intensive, process-oriented research aimed at describing the change process and the variables that support it. Process-oriented studies have tended to oversample problem drinkers with more serious problems who self-identified when recruited using community-based media solicitation. These samples thus overlap considerably with treatment-seeking samples and tend to underrepresent resolutions among persons with mild to moderate problems who do not necessarily self-label them as such and who may be more likely to become moderate drinkers. For example, in a comparison of natural remitters recruited by survey or media solicitation

methods (Rumpf, Bischof, Hapke, Meyer, & John, 2000), the media sample had more serious problems and was more likely to have abstinent resolutions, that is, only 17.3% were moderate drinkers compared to 81.1% in the survey sample.

Ironically—and almost certainly in response to similar issues embedded in the controlled drinking controversy—clinically oriented researchers have gone to great lengths to recruit participants who resembled clinical samples and to demonstrate that natural resolution occurs among persons who meet clinical criteria for alcohol dependence. This work is valuable for guiding improved clinical treatments that facilitate the natural forces that promote resolution. However, a population-based perspective on interventions (e.g., IOM, 1990; Humphreys & Tucker, 2002; Tucker et al., 1999) argues for studying the full range of persons with drinking problems who resolve naturally. Such research should aid the development of less intensive interventions that lie between clinical treatment and universal prevention, including those that support moderation in appropriate cases. At a minimum, state-of-the-art measures of drinking practices and problems should be used in survey and process-oriented studies, so that the smaller samples in the latter research can be placed within the problem drinker population, including the subsets that resolve with and without interventions.

2.2. Explicating Environment–Behavior Relations

Natural resolution research offers an opportunity to study contextual and other extratherapeutic influences on behavioral change in the absence of effects resulting from care-seeking or interventions. Research to date has relied heavily on measures of event occurrences to represent environmental variables and has yielded findings that warrant further study using better methods. For example, the event findings summarized earlier suggest that, as problem drinkers reduce their drinking, they redistribute their time and resources to other activities. Reallocation patterns that engage positive social relations and activities and take place as part of other healthy lifestyle changes seem optimal for stabilizing initial drinking behavioral change.

Shifts in behavior in domains affected by problem drinking and its resolution merit further study using measures that allow more continuous assessment of environment–behavior covariation over time than is afforded by life event scales. Such scales represent the environment as a series of punctuated events, but many contextual features are more enduring over time, and drinking patterns are embedded within them. Comprehensive schemes are needed to represent the way preferences for drinking change over time in relation to other activity opportunities (Vuchinich & Tucker, 1996). Preliminary work on this issue guided by behavioral economics (Tucker et al., 2002a) suggests that measuring the proportional allocation of resources (e.g., money, time, behavior) to drinking and other activities in the natural environment adds new information that contributes to the prediction of drinking outcomes.

A related issue that deserves further study concerns relations between relatively objective measures of environment-behavior relations and problem drinkers' lay epistemologies about influences on their drinking practices and resolution attempts. These domains should not be confused conceptually or in measurement approaches (Blomqvist, 1996; Tucker et al., 1995). For example, resolved problem drinkers often attribute positive change to increased willpower, but this self-enhancing attribution is not necessarily a causal explanation. The controlling variables of change may operate over long intervals, and problem drinkers may not discern their influence and instead attribute change to salient personal characteristics or recent events.

Finally, more molar features of the environment that are known to affect substance use deserve attention in efforts to create environments that promote natural resolution. Econometric and behavioral economic research has shown that substance use declines with increases in drug prices and other constraints on drug access and with increases in the availability of valued alternative activities that do not involve drug use (Bickel & Vuchinich, 2000; Chaloupka, Grossman, Bickel, & Saffer, 1999). Furthermore, such "environmental enrichment" deters the initial acquisition of drug use. Manipulating these molar environmental variables, as well as changing social norms so that the changeable (rather than chronic) nature of drinking problems is emphasized, may yield greater reductions in population drinking problems compared to increased treatment availability (Blomqvist, 1996; Klingemann et al., 2001). Virtually nothing is known about how these molar environmental features affect resolution patterns in individuals.

2.3. Determining Pathways to Moderation and Harm Reduction

The greater proportion of moderation outcomes among natural compared to treatment-assisted resolutions offers an opportunity to study change patterns and strategies that support moderation. Such research will help move the field beyond documenting the extent to which moderation outcomes occur in treatment evaluations to investigating how they occur naturally and under what circumstances. This will assist the development of interventions that support moderation, particularly for problem drinkers with less severe problems, including many younger adults. The abrupt initiation of abstinence that is encouraged by 12-step interventions is poorly suited to facilitating the naturally occurring incremental changes that are part of many resolutions.

Understanding the multiple and variable pathways to positive change is also central to implementing harm reduction programs that support an incremental "step-down" approach to habit change and risk reduction, even when moderation or abstinence is not possible or desired. Also, some substance abusers transit through the use of different drug classes, including alcohol, as they move in the direction of risk reduction, if not eventual abstinence. For example, some heroin addicts who eventually became drug-free had a transitional period of several years when they used other drugs, including alcohol

and marijuana (Wille, 1983). A short-term analysis would regard the other drug use as a negative outcome, rather than a reduction in the risks of harm associated with substance use as part of a lengthy resolution process. Research on this natural step-down process is lacking, except for a few studies of resolution of multiple drug abuse, including alcohol abuse and smoking (reviewed by Tucker & King, 1999).

2.4. Understanding Relations between Help-Seeking and Drinking Behavior Change

Understanding the relationship between treated and untreated cases is critical because otherwise we "risk confusing etiology with social and psychological processes leading to care" (Mechanic, 1978, p. 270). However, because natural resolution, treatment outcome, and help-seeking literatures developed fairly independently, little is known about (1) how influences on behavioral change and help-seeking processes may differ, (2) how the processes may interact with one another and with problem drinkers' ongoing life circumstances, and (3) how interventions may promote positive change in different dimensions of problem drinking at variable points in the resolution process. These research questions are fundamental to Mechanic's distinction and highlight the need to investigate the change process and the circumstances that support it among problem drinkers with different help-seeking experiences. As summarized earlier, the few relevant studies (e.g., Tucker et al., 1996, 2002b) revealed both common and unique components of change among different help-seeking groups, and integrative reviews of the help-seeking and behavioral change literatures (e.g., Marlatt et al., 1997; Tucker, 2001; Tucker & King, 1999) reached similar conclusions.

Research on these topics will necessarily involve designs that extend beyond the dominant, randomized controlled clinical trial (RCT), or "efficacy," approach to studying treatment-produced change to include naturalistic, descriptive studies of change in problem drinkers with different help-seeking experiences (including none) (Humphreys & Tucker, 2002). Treatment outcome studies have contributed much knowledge about behavioral change but have limitations due to their use of treatment samples and the artificial constraints they place on the help-seeking and treatment engagement process. Moreover, they focus on a single help-seeking episode and thus cannot study temporal relations between help-seeking and changes in drinking and related problems during the course of individual drinking careers. Analysis of relations over a more extended time frame is important because many problem drinkers drink more in and out of periods of abusive drinking. How this variability in drinking covaries with the use of interventions and with the surrounding environmental contexts is poorly understood.

Treatment outcome studies also cannot address the help-seeking problem, which must be understood and solved if the array of useful interventions for drinking problems is to be marketed effectively to consumers of services.

Naturalistic studies of help-seeking and resolution processes and outcomes ("effectiveness" and related research) are needed to complement findings from RCTs (Tucker, 1999).

3. Conclusions

The diverse research discussed here, ranging from surveys to RCTs to process-oriented naturalistic studies, converged to raise previously overlooked research questions about relations between patterns of help-seeking and drinking problem resolutions. Contrary to conventional views, treatment is neither a necessary nor a sufficient condition for resolution, which can occur through a number of pathways and is influenced by extratherapeutic contextual variables. Further research on the variable course of resolutions, the surrounding contexts, and relations with help-seeking holds promise for informing the development of a range of interventions for drinking problems across the continuum of severity and for increasing their appeal.

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References

- American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: Author.
- Armor, D.J., & Meshkoff, J.E. (1983). Remission among treated and untreated alcoholics. In N.K. Mello (ed.), *Advances in Substance Abuse: Behavioral and Biological Research*. Greenwich, CT: JAI Press, Vol. 3, pp. 239–269.
- Bickel, W.K., & Vuchinich, R.E. (eds.) (2000). *Reframing Health Behavior Change with Behavioral Economics*. Mahwah, NJ: Erlbaum.
- Blomqvist, J. (1996). Paths to recovery from substance misuse: Change of lifestyle and the role of treatment. *Substance Use & Misuse* 31, 1807–1852.
- Chaloupka, F.J., Grossman, M., Bickel, W.R., & Saffer, H. (eds.) (1999). *The Economic Analysis of Substance Use and Abuse: An Integration of Econometric and Behavioral Economic Research*. (A National Bureau of Economic Research Conference Report.) Chicago, IL: University of Chicago Press.
- Crawford, A.L., & Tucker, J.A. (2002). Life events surrounding behavior change efforts and treatment entry among women with bulimia nervosa. Submitted for review.
- Cunningham, J.A., Sobell, L.C., Sobell, M.B., Agrawal, S., & Toneatto, T. (1993). Barriers to treatment: Why alcohol and drug abusers delay or never seek treatment. *Addictive Behaviors* 18, 347–353.
- Dawson, D.A. (1996). Correlates of past-year status among treated and untreated persons with former alcohol dependence: United States, 1992. *Alcoholism: Clinical and Experimental Research* 20, 771–779.
- Eysenck, H. (1952). The effects of psychotherapy: An evaluation. *Journal of Consulting Psychology* 16, 319–324.
- Fillmore, K.M. (1988). *Alcohol Use Across the Life Course: A Critical Review of 70 Years of International Longitudinal Research*. Toronto: Addiction Research Foundation.
- Fortney, J.C., Booth, B.M., & Curran, G.M. (1999). Do patients with alcohol dependence use more services? A comparative analysis with other chronic disorders. *Alcoholism: Clinical and Experimental Research* 23, 127–133.

- Grant, B.F. (1996). Toward an alcohol treatment model: A comparison of treated and untreated respondents with DSM-IV alcohol use disorders in the general population. *Alcoholism: Clinical and Experimental Research* 20, 372-378.
- Hilton, M.E. (1987). Drinking patterns and drinking problems in 1984: Results from a general population survey. *Alcoholism: Clinical and Experimental Research* 11, 167-175.
- Hodgins, D.C., El-Quebaly, N. (2000). Natural and treatment-assisted recovery from gambling problems: A comparison of resolved and active gamblers. *Addiction* 95, 777-789.
- Humphreys, K., & Tucker, J.A. (2002). Toward more responsive and effective intervention systems for alcohol-related problems. *Addiction* 97, 126-132.
- Humphreys, K., & Weisner, C. (1999, June). The one-year course of alcohol dependence in a community sample. Presented at the meeting of the *Research Society on Alcoholism*, Santa Barbara, CA.
- Humphreys, K., Moos, R.F., & Finney, J.W. (1995). Two pathways out of drinking problems without professional treatment. *Addictive Behaviors* 20, 427-441.
- Institute of Medicine (1990). *Broadening the Base of Treatment for Alcohol Problems*. Washington, DC: National Academy Press.
- King, M.P., & Tucker, J.A. (1998). Natural resolution of alcohol problems without treatment: Environmental contexts surrounding the initiation and maintenance of stable abstinence or moderation drinking. *Addictive Behaviors* 23, 537-541.
- King, M.P., & Tucker, J.A. (2000). Behavior change patterns and strategies distinguishing moderation drinking and abstinence during the natural resolution of alcohol problems without treatment. *Psychology of Addictive Behaviors* 14, 48-55.
- Klingemann, H.K.-H. (1991). The motivation for change from problem alcohol and heroin use. *British Journal of Addiction* 86, 727-744.
- Klingemann, H., Sobell, L., Barker, J., Blomqvist, J., Cloud, W., Ellinstad, T., Fingfeld, D., Granfield, R., Hodgins, D., Hunt, G., Junker, C., Moggi, F., Peele, S., Smart, R., Sobell, M., & Tucker, J. (2001). *Promoting Self-Change from Problem Substance Use: Practical Implications for Prevention, Policy and Treatment*. Dordrecht, The Netherlands: Kluwer Academic.
- Levenson, M.R., Aldwin, C.M., & Spiro, A. (1998). Age, cohort and period effects on alcohol consumption and problem drinking: Findings from the Normative Aging Study. *Journal of Studies on Alcohol* 59, 712-722.
- Luborsky, L., Singer, B., & Luborsky, L. (1975). Comparative studies of psychotherapies: Is it true that "everyone has won and all must have prizes"? *Archives of General Psychiatry* 32, 995-1008.
- Maisto, S.A., Sobell, L.C., Sobell, M.B., Lei, H., & Sykora, K. (1988). Profiles of drinking patterns before and after outpatient treatment for alcohol abuse. In T. Baker & D. Cannon (eds.), *Assessment and Treatment of Addictive Behaviors*. New York: Praeger, pp. 3-27.
- Mariezcurrena, R. (1994). Recovery from addictions without treatment: Literature review. *Scandinavian Journal of Behaviour Therapy* 23, 131-154.
- Marlatt, G.A., Tucker, J.A., Donovan, D.M., & Vuchinich, R.E. (1997). Help-seeking by substance abusers: The role of harm reduction and behavioral-economic approaches to facilitate treatment entry and retention. In L.S. Onken, J.D. Blaine, & J.J. Boren (eds.), *Beyond the Therapeutic Alliance: Keeping the Drug-Dependent Individual in Treatment* (National Institute on Drug Abuse Monograph No. 165). Rockville, MD: U.S. Dept. of Health and Human Services, National Institutes of Health, pp. 44-84.
- Mechanic, D. (1978). *Medical Sociology*, 2nd ed. New York: The Free Press.
- Miller, W.R., & Page, A.C. (1991). Warm turkey: Other routes to abstinence. *Journal of Substance Abuse Treatment* 8, 227-232.
- Narrow, W.E., Regier, D.A., Rae, D.S., Manderscheid, R.W., & Locke, B.A. (1993). Use of services by persons with mental and addictive disorders. *Archives of General Psychiatry* 50, 95-107.
- Peele, S. (1993). *The Diseasing of America: Addiction Treatment out of Control*. Boston, MA: Houghton Mifflin.
- Prochaska, J.O., DiClemente, C.C., & Norcross, J.C. (1992). In search of how people change: Applications to addictive behaviors. *American Psychologist* 47, 1102-1114.
- Regier, D.A., Narrow, W.E., Rae, D.S., Manderscheid, R.W., Locke, B.A., & Goodwin, F.K. (1993). The de facto U.S. mental and addictive disorders service system. *Archives of General Psychiatry* 50, 85-94.

- Robins, L.N. (1993). Vietnam veterans' rapid recovery from heroin addiction: A fluke or normal expectation? *Addiction* 88, 1041–1054.
- Robins, L.N., Helzer, J.E., & Davis, D.H. (1975). Narcotic use in Southeast Asia and afterward. *Archives of General Psychiatry* 32, 955–961.
- Roizen, R., Cahalan, D., & Shanks, P. (1977). "Spontaneous remission" among untreated problem drinkers. In D.B. Kandel (ed.), *Longitudinal Research on Drug Use*. Washington, DC: Hemisphere, pp. 197–221.
- Roizen, R., & Fillmore, K.M. (2001). Some notes on the new paradigmatic environment of "natural remission" studies in alcohol research. *Substance Use & Misuse* 36, 1443–1466.
- Room, R. (1977). Measurement and distribution of drinking patterns and problems in general populations. In G. Edwards, M.M. Gross, M. Keller, J. Moser, & R. Room (eds.), *Alcohol-Related Disabilities*. Geneva, Switzerland: World Health Organization, pp. 61–87.
- Rosenberg, H. (1993). Prediction of controlled drinking by alcoholics and problem drinkers. *Psychological Bulletin* 113, 129–139.
- Rumpf, H.-J., Bischof, G., Hapke, U., Meyer, C., & John, U. (2000). Studies on natural recovery from alcohol dependence: Sample selection bias by media solicitation? *Addiction* 95, 765–775.
- Schachter, S. (1982). Recidivism and self-cure of smoking and obesity. *American Psychologist* 37, 436–444.
- Schmidt, L.A., & Weisner, C.M. (1999). Public health perspective on access and need for substance abuse treatment. In J.A. Tucker, D.M. Donovan, & G.A. Marlatt (eds.), *Changing Addictive Behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford, pp. 67–96.
- Smart, R.G. (1975/76). Spontaneous recovery in alcoholics: A review and analysis of the available research. *Drug and Alcohol Dependence* 1, 277–285.
- Sobell, L.C., Cunningham, J.A., & Sobell, M.B. (1996). Recovery from alcohol problems with and without treatment: Prevalence in two population surveys. *American Journal of Public Health* 86, 966–972.
- Sobell, L.C., Ellingstad, T.P., & Sobell, M.B. (2000). Natural recovery from alcohol and drug problems: Methodological review of the research with suggestions for future research. *Addiction* 95, 749–764.
- Sobell, L.C., Sobell, M.B., & Toneatto, T. (1992). Recovery from alcohol problems without treatment. In N. Heather, W.R. Miller, & J. Greeley (eds.), *Self-Control and Addictive Behaviors*. New York: Maxwell Macmillan, pp. 192–242.
- Sobell, M.B., & Sobell, L.C. (1999). Stepped care for alcohol problems: An efficient method for planning and delivering clinical services. In J.A. Tucker, D.M. Donovan, & G.A. Marlatt (eds.), *Changing Addictive Behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford, pp. 331–343.
- Stall, R., & Biernacki, P. (1986). Spontaneous remission from the problematic use of substances: An inductive model derived from a comparative analysis of the alcohol, opiate, tobacco, and food/obesity literatures. *International Journal of the Addictions* 21, 1–23.
- Tinker, J.E., & Tucker, J.A. (1997). Environmental events surrounding natural recovery from obesity. *Addictive Behaviors* 22, 571–575.
- Tuchfeld, B.S. (1980). Spontaneous remission in alcoholics: Empirical observations and theoretical implications. *Journal of Studies on Alcohol* 56, 597–610.
- Tucker, J.A. (1995). Predictors of help-seeking and the temporal relationship of help to recovery among treated and untreated recovered problem drinkers. *Addiction* 90, 805–809.
- Tucker, J.A. (1999). Changing addictive behavior: Historical and contemporary perspectives. In J.A. Tucker, D.M. Donovan, & G.A. Marlatt (eds.), *Changing Addictive Behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford, pp. 3–44.
- Tucker, J.A. (2001). Resolving alcohol and drug problems with and without interventions: Understanding relations between addictive behavior change and the use of services. *Substance Use & Misuse* 36, 1501–1518.
- Tucker, J.A., & King, M.P. (1999). Resolving alcohol and drug problems: Influences on addictive behavior change and help-seeking processes. In J.A. Tucker, D.M. Donovan, & G.A. Marlatt (eds.), *Changing Addictive Behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford, pp. 97–126.

- Tucker, J.A., Vuchinich, R.E., & Gladsjo, J.A. (1990/91). Environmental influences on relapse in substance use disorders. *International Journal of the Addictions* 25, 1017–1050.
- Tucker, J.A., Vuchinich, R.E., & Gladsjo, J.A. (1994). Environmental events surrounding natural recovery from alcohol-related problems. *Journal of Studies on Alcohol* 55, 401–411.
- Tucker, J.A., Vuchinich, R.E., & Pukish, M. (1995). Molar environment contexts surrounding recovery from alcohol problems by treated and untreated problem drinkers. *Experimental and Clinical Psychopharmacology* 3, 195–204.
- Tucker, J.A., Donovan, D.M., & Marlatt, G.A. (eds.) (1999). *Changing Addictive Behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford.
- Tucker, J.A., Vuchinich, R.E., & Rippens, P.D. (2002a). Predicting natural resolution of alcohol-related problems: A prospective behavioral economic analysis. *Experimental and Clinical Psychopharmacology* 10, 248–257.
- Tucker, J.A., Vuchinich, R.E., & Rippens, P.D. (2002b). Environmental contexts surrounding resolution of drinking problems among problem drinkers with different help-seeking histories. *Journal of Studies on Alcohol* 63, 334–341.
- Vuchinich, R.E., & Tucker, J.A. (1996). The molar context of alcohol abuse. In L. Green & J.H. Kagel (eds.), *Advances in Behavioral Economics*, Vol. 3: *Substance Use and Abuse*. Norwood, NJ: Ablex, pp. 133–162.
- Walters, G.D. (2000). Spontaneous remission from alcohol, tobacco, and other drug abuse: Seeking quantitative answers to qualitative questions. *American Journal of Drug and Alcohol Abuse* 26, 443–464.
- Watson, A.L., & Sher, K.J. (1998). Resolution of alcohol problems without treatment: Methodological issues and future directions of natural recovery research. *Clinical Psychology: Science and Practice* 5, 1–18.
- Wille, R. (1983). Processes of recovery from heroin dependence: Relationship to treatment, social changes and drug use. *Journal of Drug Issues* 13, 333–342.
- Williams, G.D., & DeBakey, S.F. (1992). Change in level of alcohol consumption in the United States, 1983–1988. *British Journal of Addiction* 87, 333–342.

III

Psychosocial Treatments

Richard K. Fuller, Section Editor

Overview

Richard K. Fuller

This section is entitled Psychosocial Treatments. This term is commonly used for any treatment that is not a pharmacological treatment. Consequently, a broad array of therapies is reviewed in this section. This author has never liked the term because it brings to his mind a treatment that is part psychological and part social, whatever is meant by social. However, there are no good alternative terms. Some have used the term verbal therapies to capture the full range of counseling techniques. The National Institutes of Health often lump all of these counseling techniques under the label of behavioral therapies while acknowledging that the term behavioral is being broadly used. Fortunately, the authors of these excellent chapters are not distracted by terminology. These authors have all been leaders in research on the treatments they discuss, and they have produced scholarly reviews that give the current status of and the evidence for or against the efficacy of the treatments they are discussing. This is very valuable for clinicians. They also describe directions that future research should take. This is valuable for researchers.

Dr. Kadden's chapter entitled "Behavioral and Cognitive Behavioral Treatments" reviews those therapies that fit the more standard definition of behavioral therapies, that is, the theoretical basis for them is rooted in social learning theory. Dr. Kadden begins with two strictly behavioral therapies, cue exposure and contingency management, before reviewing coping skills training, relapse prevention, and behavioral marital therapy. As Dr. Kadden points out, coping skills training and relapse prevention take into account cognitive and emotional antecedents and expectancies as well as behavior.

Generally, these therapies have been evaluated more frequently in controlled clinical trials than in 12-step approaches. Yet, the 12-step approaches are

far more commonly used in treatment by treatment programs than the behavioral therapies. An exception is relapse prevention which many programs use. However, the relapse prevention used in many programs has been modified to fit in with 12-step approaches. In discussing coping skills training, Dr. Kadden discusses the reasons that may explain why coping skills training which has been extensively studied in controlled trials is not used by most treatment programs.

A behavioral therapy of interest to this author is behavioral marital therapy. This is because of the work of Timothy O'Farrell and his colleagues whose study¹ of behavioral marital therapy following more standard treatment showed a striking reduction in domestic violence. Dr. Kadden points out some limitations to couples therapy, but I think that treatment program staffs should learn more about this therapy and give thought to incorporating it into their programs where appropriate. This issue is also discussed in Dr. Longabaugh's chapter.

Dr. DiClemente and his colleagues review the psychological therapies of "psychosocial" treatments. These include psychodynamic treatments, interpersonal psychotherapy, cognitive therapy, and motivation enhancement. Motivational enhancement techniques vary from brief versions for patients with alcohol problems (but not dependence) to more extensive versions, such as Motivational Enhancement Therapy, used in Project MATCH for alcohol-dependent individuals. Motivational Enhancement Therapy is currently attracting considerable interest among treatment providers. DiClemente et al. review the literature on using motivational interviewing techniques for both alcohol-dependent patients and those with problems from alcohol. For the latter, they review the results from studies done in obstetric clinics, inpatient trauma units, and emergency departments. This type of counseling in medical settings is called brief intervention because the sessions are usually one to four in number and are brief in time. The use of brief interventions in medical settings has important public health implications.

Dr. DiClemente and associates reviewed the psychological part of "psychosocial," and Drs. Meyers, Smith, and Lash review the Community Reinforcement Approach (CRA) which explicitly posits that a person's recovery is affected by his or her environment—family, friends, work, social activities. So CRA emphasizes the social aspect of "psychosocial." The chapters on support networks by Dr. Longabaugh and self-help groups by Dr. Humphreys also review therapies that use supportive social networks. However, theoretically, CRA is broader in using environmental factors in aiding recovery. Drs. Meyers, Smith, and Lash also describe how the CRA approach can be adapted to help families and friends assist individuals who are opposed to treatment to enter treatment.

The Community Reinforcement Approach also illustrates that there is often overlap among psychosocial treatments. The Community Reinforcement Approach begins with a functional analysis of drinking behavior. This is like Motivational Enhancement Therapy. CRA also identifies internal and external triggers for relapse. Sounds like Cognitive Behavioral therapy! There is much more to CRA than these elements, but it illustrates the point.

Dr. Longabaugh also reviews therapies that emphasize the social more than psychological. He makes the case that over the long haul the patient's recovery is more related to his or her social network than short-term treatment, either psychological counseling or pharmacotherapy. This discussion inevitably includes self-help groups, but Dr. Longabaugh excludes Alcoholics Anonymous (AA) because AA is reviewed in Dr. Humphreys' chapter. Although many people may be part of one's social environment, Dr. Longabaugh primarily limits his review to spouse, family, and friends ("buddies") because there is little research on other members of the broader social environment. This examination of the social network leads to a review of studies that looked at improving the relationship between a significant other, usually the spouse, and the patient to achieve the goal of reducing the patient's alcohol consumption.

Dr. Humphreys continues the review of social networks by reviewing the literature on Alcoholics Anonymous (AA) and 12-step treatment programs. He points out that though AA is the most commonly used component in the United States treatment system and has strongly influenced professional treatment programs, the number of longitudinal evaluative studies is modest. Dr. Humphreys uses the available literature to give us an idea of the effectiveness of AA and professional 12-step programs. Also, importantly, he reviews the literature on the therapeutic processes in mutual-help groups that appear to be responsible for their effectiveness. These results are very interesting. To date, it has not been found that spirituality is as an important mediator between 12-step treatment and outcome as other factors. Either spirituality is not as critical as 12-step adherents believe, or scientists lack the ability to measure it accurately.

Appropriately, Dr. Humphreys devotes space to the findings on Twelve Step Facilitation (TSF) from Project MATCH and describes the one primary patient-treatment match that was found. It is worth noting, however, that the Project MATCH investigators developed 21 a priori potential patient-treatment matches to test. They then divided the 21 a priori matches into 10 primary matches and 11 secondary matches. Ten were designated primary because the Project MATCH investigators thought that the chances of finding a match in the set of 10 primary matches were greater than in the set of 11 secondary matches, and by analyzing them 10 initially would enhance statistical power.

However, two matches involving TSF were found in the a priori secondary set. One match was that aftercare patients higher in severity of alcohol dependence, who were treated with TSF, had better treatment outcomes. Aftercare patients were those initially treated with at least 10 days of inpatient or residential treatment before receiving the Project MATCH interventions as outpatients. Another match was found in the outpatients, that is, those who had no recent previous inpatient or residential treatment and were treated exclusively as outpatients. This match was found at the 3-year follow-up. The match was that patients who had a social network supportive of drinking at the time of entering treatment had better outcomes if treated with TSF.

I am going to take this opportunity to make a personal observation about AA members. Thirty-four years ago, I became involved in treating alcoholics.

The counselors I worked with were all active in AA. I have always admired the dedication of active AA members and have a warm spot in my heart for AA. Yet there is an unfortunate tendency of some AA members to close their minds to other therapeutic approaches. Since alcoholism treatment is not 100% successful, we will improve our therapeutic efforts only if we are open to other therapies that have been found effective in rigorously controlled research.

Project MATCH found few outcome differences among the three treatments used in that study. The equivalency among therapies and the fact that individual treatments helped some but not all individuals had been noted before. So the concept developed that treatment outcome could be improved if we could better match patients, on the basis of their characteristics, to specific treatments. Such information should be very important in treatment planning. The concept of patient-treatment matching led to Project MATCH. Surprisingly, the results of Project MATCH only weakly supported the concept of patient-treatment matching. Dr. Mattson reviews the matching literature since Project MATCH and comes to interesting conclusions.

I hope this brief overview provides a sense of the important information found in these chapters. Enjoy!

Reference

1. O'Farrell, T.J., Van Hutton, V., & Murphy, C.M. (1999). Domestic violence before and after alcoholism treatment: A two-year longitudinal study. *Journal of Studies on Alcoholism* 60, 317-321.

The Search for a Rational Basis for Treatment Selection

Margaret E. Mattson

1. Overview of Models of Treatment Selection

It is timely to assess where the alcoholism treatment research field stands in its search for a rational basis for individualizing treatment selection, or as it is frequently called, "patient-treatment matching." The purpose of this review is to summarize models and results of research on optimizing treatment selection published after 1997 when the unexpected results of Project MATCH took the field by surprise. The concluding section will consider the future prospects for research on treatment selection approaches in the light of current knowledge.

One finds a variety of terms in the research literature reflecting the continued search for a strategy to guide the choice of treatment from among the reasonably effective therapies available. These terms include matching, tailoring, individualization of treatment, treatment decision-making, treatment planning, patient placement criteria, use of nonroutinized treatments, and optimization of treatment assignment. The underlying models have varied, on one hand, from unitary approaches linking a single patient characteristic with a particular treatment to fully prescriptive approaches that consider the contributions of a host of personal, environmental, and temporal factors.

Examples of strategies of models intermediate between these two extremes include (1) sequencing treatment components according to the individual's stage of readiness and varying the approach as needed over time and (2) assigning treatment in a stepped care fashion in which treatment is initiated by using the least intense/costly treatment likely to address the patients needs, with the option of moving to higher levels if treatment is unsuccessful. Still other strategies

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advocate a human services approach and seek to improve on fixed programs that may lack the flexibility to provide necessary ancillary support services. Hybrid models integrate several approaches and offer placement criteria that follow a modified prescriptive approach and define a matrix of patient characteristics versus levels of care, incorporating notions of stepped care, patient readiness, resources, and context. The level and type of validation of the various extant models vary greatly. Supportive evidence includes theoretical justification, experience from other disorders, clinical experience, naturalistic studies, secondary analysis of databases, and randomized clinical trials.

Regardless of the specifics, the goals of the various models are the same: to prescribe treatment that will engage and retain the client, be efficacious, and make the best use of available resources. The remainder of this section reviews models reported in the literature between approximately 1997 and the present. Models are classified into two main categories: (1) those based on matching to a single patient characteristic assessed before treatment and (2) those based on matching to multiple dimensions of the patient and/or environment, assessed before, and perhaps also during, the treatment process.

2. Treatment Selection Models Based on Single Patient Characteristics

2.1. Single Patient Characteristics Matched to Behavioral Interventions

The approach of prescribing a particular type of treatment according to a single pretreatment characteristic of the client was prominent in the matching literature of the 1970s through the mid-1990s. A range of patient characteristics covering clinical, social, psychological, behavioral, and spiritual domains has been reported and reviewed (Mattson, Allen, Longabaugh, Nickless, Connors, & Kadden, 1994; Allen & Kadden, 1995). By the late 1980s the number and variety of matches were encouraging, and providers sought definitive guidance on their application in practice. The need to validate the matches found in the single site studies and to test the generic matching hypothesis in a large, multisite clinical trial prompted the launching of Project MATCH in 1989. This section will briefly summarize the main matches reported by Project MATCH and then go on to describe other findings based on single patient characteristics reported since 1997.

2.1.1. Matches Reported by Project MATCH. Project MATCH examined 21 patient characteristics and their ability to predict effective matches in relation to three conceptually distinct, manual-driven therapies delivered individually by professional therapists: Cognitive Behavioral Therapy (CBT), Motivational Enhancement Therapy (MET), and Twelve Step Facilitation Therapy (TSF). (Project MATCH Research Group, 1993.) Hypothesized matches were specified *a priori* and described in terms of underlying theory and postulated mechanisms

of action. The latter refers to the sequence of intermediate mediator and moderator variables believed necessary for the therapeutic action to occur. The Project MATCH Research Group reported the results in 1997 (a,b) and 1998 (b), as did Longabaugh, Wirtz, Zweben, and Stout in 1998. These results have been reviewed in detail elsewhere (Project MATCH Research Group, 1998a; Mattson, 1998; Babor, 1999).

Contrary to the expectations generated by previous smaller scale studies, relatively few matches between single patient characteristics and the three treatments emerged. Many hypothesized matches were not supported and those found were, for the most part, of rather modest magnitude and often varied over time, between arms of the trial, and for the two primary outcome measures. A total of 4 of the 21 patient variables studied showed plausible matches. The three matches in the outpatient arm involved *psychiatric severity*, *client anger*, and *social network support for drinking*, and, in the aftercare arm, *alcohol dependence*. Features of these matches are summarized in Table 1.

2.1.2. Disorder Severity and Treatment Intensity. In 1998, Thornton, Gottheil, Weinstein and Kerachsky reported on a mixed sample of 60 substance-dependent

Table 1. Summary of Matches Reported by Project MATCH

Patient Variable	Matched Treatment	Description of the Match
Low psychiatric severity	TSF ^a	Outpatient arm only. Low psychiatric severity patients had more abstinent days as compared to CBT ^b for several months during the follow-up period. Largest difference was at month 6 when TSF patients had 87% days abstinent versus 73% in CBT. Effect did not persist at 3-year followup.
High anger	MET ^c	Outpatient arm only. Matched patients abstinence differential was 9% (i.e., 85% vs. 76%); When they did drink, patients drank less intensely. Effect lasted throughout the 1 year after treatment and was also present at the 39-month follow up. Most consistent matching result across time.
Social network supportive of drinking	TSF	Outpatient arm only. Those in TSF did better than MET group. Late effect: seen only at the 3-year follow up. TSF group was abstinent 83% of days versus 66% for MET. Largest difference observed in Project MATCH. The higher AA attendance in the TSF as compared to MET may have played a role.
High alcohol dependence	TSF	Aftercare arm only. Patients highest in dependence were abstinent on 94% of posttreatment days when treated with TSF vs. 84% for those in CBT. Consistent for posttreatment period of 15 mo.

^aTSF = Twelve Step Facilitation Therapy.

^bCBT = Cognitive Behavioral Therapy.

^cMET = Motivational Enhancement Therapy.

patients randomly assigned to 12 weeks of either a high-structure, behaviorally oriented treatment or low-structure, facilitative individual counseling. Results on treatment attendance, problem severity, and substance use during treatment were consistent with their hypothesis that more severe patients would benefit more from the high-structure, behaviorally oriented therapy and vice versa.

In contrast to the results of Thornton et al. (1998) are those reported by Trent in 1998 with a large ($n = 2,823$) study of active duty Navy service personnel. The study was conducted from 1992–1994 in one-half of the Navy's residential alcoholism treatment facilities, where treatment is built upon a basic AA platform. The purpose was to compare participants in the standard 6-week program with those given a similar, but shortened, 4-week program. Treatment assignment was not randomized but was based on when during the study period the patient entered treatment. There were no significant interactions between patient predictors and the length of the treatment program. Rather, months of aftercare attendance was the single best predictor of outcome variance, underscoring the importance of continuing support for alcoholics in recovery. Trent comments that his results may be unique in that his population was mostly young, white, male personnel who tended to be less severe in their alcohol usage and had better prognostic assets than typical civilian inpatient clients.

Rychtarik, Connors, Whitney, McGillicuddy, Fitterling, and Wirtz (2000) randomly assigned 192 participants to one of three treatment settings: inpatient, intensive outpatient, and standard outpatient. Clients high in alcohol involvement (as determined by the AUI) benefited more from inpatient than from outpatient care, and the opposite was true for the low alcohol involvement clients. Likewise, clients with low cognitive functioning did better with inpatient care than outpatient. No matching was seen for the social support for drinking variable. They concluded that inpatient treatment may be preferred for patients with more severe alcohol problems and/or cognitive impairment.

2.1.3. Psychiatric Diagnoses and Individual versus Relationally Oriented Therapy. Kalman, Longabaugh, Clifford, Beattie, and Maisto (2000) attempted to replicate an earlier study which found that alcoholics with antisocial personality disorder did somewhat better if they received individually focused cognitive behavioral therapy, compared to relationship-focused community reinforcement. In a randomized study, 149 alcoholics (28% of whom scored high in sociopathy) were followed for 2 years. The authors found no difference in outcome in the two treatment conditions.

Kadden, Litt, Cooney, Kabela, and Getter (2001) investigated whether outcomes were improved by matching among patients characterized according to psychiatric severity and sociopathy. Based on previous results, they hypothesized that those low on both factors would do better in interactional group therapy and those higher would benefit more from the cognitive behavioral modality. This replication in 250 patients failed to show an advantage in drinking outcomes for matching based on these patient characteristics. They noted, however, that those

prospectively matched did have fewer negative consequences of drinking than the randomly assigned, unmatched patients.

2.1.4. Type A/Type B Alcoholics and Interactional versus Coping Therapy. Ball, Jaffe, Crouse-Artus, Rounsville, and O'Malley (2000), using cluster analysis to define multidimensional subtypes, classified a group of 246 first-time DWI offenders into Type A and B consistent with other classifications of A/B alcoholics, that is, Type B's have greater evidence of premorbid risk factors, greater substance abuse severity and psychosocial impairment. Participants were randomly assigned to either DWI Education, Coping Skills, or Interactional Therapy, each a 10-week intervention. No matching effects were evident at the end of treatment, at 6 months, and 1 year, consistent with Project MATCH findings.

2.1.5. Conceptual Level and Treatment Structure. In a study of 119 alcoholics, Neilsen (1998) studied whether patients randomly assigned to low- or high-structured treatments for 12 months had different compliance outcomes based on their baseline conceptual level score. Those patients correctly matched to treatment structure had a higher compliance rate (63%) during treatment than mismatched patients (38%) by the end of the 12-month treatment period. By comparison, Project MATCH found no differential in drinking outcomes based on conceptual level.

2.1.6. Personality Profiles and Tailored Motivational Interventions. Conrod et al. (2000) studied 198 female substance abusers randomly assigned to one of three forms of brief (i.e., 90-minute session) interventions consisting of (1) a personality specific motivation and coping skills, (2) a control intervention involving a motivational film and supportive discussion with a therapist, or (3) a mismatched motivational interview targeted to a personality profile different from that of the patient. Follow-up assessment done 6 months later measured alcohol and drug use, dependence symptoms, use of other mental health services since the intervention, and self-reported concerns about current substance use. The matched intervention had an outcome advantage over and above the generic effects of the motivational interview. Matching enhanced improvement in the frequency and severity of problematic alcohol and drug use. For example, those in the matched group attained an abstinence rate of 23%, compared to 6% in the control group and 11% in the mismatched group.

2.1.7. Emotional Distress/Reactance. Korno (2002) reported on interactions between patient characteristics and therapist variables in his study of 47 patients who received one of two treatments, Cognitive Behavioral Therapy or Family Systems. Interactions between patient characteristics and the type of therapy were not predictive of alcohol use. However, patients high in emotional distress had better drinking outcomes when their therapy addressed their

emotional experiences; the opposite occurred in patients with low distress. A second finding was that patients high in reactance did better when their therapy was delivered in a nondirective manner, whereas those low in reactance did better with more directed therapy.

2.2. Single Patient Characteristics Matched to Pharmacological Therapies

Although the vast majority of alcoholics are treated by behavioral or verbal types of therapies, in the past 10 years the interest in treating alcoholism with pharmacological agents has grown considerably. The body of data pointing to the potential of pharmacological agents as aids in treating alcoholism has been reviewed extensively (e.g., Litten & Allen, 1998; Kranzler, 2000). Several classes of drugs are being studied, including opiate antagonists, selective serotonin reuptake inhibitors (SSRIs), and glutameric agents. Since 1996, approximately 10 studies have reported on interactions between patient characteristics and pharmacological agents and are summarized below.

2.2.1. Comorbidity: Alcoholics with Depression or Anxiety. Mason, Kocsis, Ritvo, and Cutler reported in 1996 that the use of the antidepressant, desipramine, may reduce the risk of relapse in depressed alcoholics but not in the nondepressed. In a similar vein, Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase, and Black (1997) found that fluoxetine, a SSRI, reduced depressive symptoms and alcohol intake in a 3-month trial of 51 severe inpatient alcoholics with major depression and suicide risk. In 2000, Cornelius, Salloum, Haskett, Daley, Cornelius, Thase and Perel reported on interviews of 31 of the original patients about 9 months after finishing the trial; during that time, about 75% had been maintained by their private physicians on the same regime (i.e., either fluoxetine or no antidepressant). The improvements in symptoms of depression and alcohol intake attained during the initial acute treatment were largely maintained, arguing for, the authors suggest, a 12-month course of treatment for depressed alcoholics. However, Pettinati, Volpicelli, Kranzler, Luck, Rukstalis, and Cnaan (2001) and McGrath, Nunes, and Stewart (1998) found that fluoxetine and sertraline were no better than placebo in improving depression and reducing drinking in less severely depressed alcoholics.

In a study of anxious alcoholics, Kranzler, Burleson, DelBoca, Babor, Korner, Brown, and Bohn (1994) found that buspirone appeared more helpful to those higher in anxiety. However, in the earlier (1992) study of Malcom, Anton, Randall, Johnson, Brady, and Thevos, this effect was not observed.

2.2.2. Type A/B Alcoholics. In 2000, Johnson, Roache, Javors, DiClemente, Cloninger, Prihoda, Bordnick, Ait-Daoud, and Hensler studied the effect of the 5-HT₃ antagonist, ondansetron, on drinking in early versus later onset alcoholics. Early onset alcoholics were defined as those who showed drinking problems earlier in life, had antisocial characteristics, and had a family history

of the disorder in first-degree relatives. They found that ondansetron reduced drinking preferentially in the early onset group. In a small pilot study also in 2000, Johnson, Ait-Daoud, and Prihoda combined ondansetron with naltrexone and found that the combination reduced alcohol consumption in the early onset group to a larger degree than either of the two medications alone. Interestingly, Kranzler, Burleson, Brown, and Babor (1996) and Pettinati, Volpicelli, Kranzler, Luck, Ruckstalis, and Cnaan (2000) showed that higher risk, higher severity, Type B alcoholics did less well on SSRIs than lower risk, lower severity, Type A alcoholics.

2.2.3. High Craving and Low Cognitive Function. Jaffe, Rounsville, Chang, Schottenfeld, Meyer, and O'Malley subjected data from initial studies of the efficacy of naltrexone for the treatment of alcoholism to subsequent post hoc analyses in 1996. The authors concluded that naltrexone appears more beneficial for alcoholics with high craving and poorer cognitive functioning.

3. Multidimensional Models of Patient Selection

3.1. *Matching Based on Client Resource Needs and Program Services*

McLellan's group (1997) and others have pointed out that many substance abuse patients have life problems related to their addiction, such as medical, job, financial, family, legal, or psychiatric difficulties, that must be addressed during treatment. Failing to address these needs may obviate even the most careful substance abuse treatment. It has been argued that social and environmental services should be a separate dimension of care not necessarily incorporated within clinical services and that matching should be based on both types of needs (McGee & Mee-Lee, 1997). Care models that "bundle" or link clinical services intensity with a predetermined set of supports may miss the mark by providing unneeded services in some cases and insufficient or inappropriate services in others.

Reviewers (McLellan & McKay, 1998) have concluded that those with more severe problems who receive specialized adjunctive help for these problems show improved function in these areas after treatment, although there is not necessarily a relationship to reduced substance use. McLellan and colleagues (1997) identified problems and needs of 94 substance abuse patients randomly assigned to four treatment programs and attempted to match professional services related to psychiatric, family, or employment problems. Patients matched to needed services had better treatment retention and improved outcomes in problem areas and substance use than patients treated in the same programs but without services.

In an observational study matching client needs and program services with outcomes, 171 clients with drug or drug/alcohol addictions were asked if they wished to receive any of a list of 30 services at intake. At the follow-up

interview, they were asked which of the list of services they had received (Hser, Polinsky, Maglione, & Anglin, 1999). Matching certain types of services (vocational, childcare, housing, and transportation) improved retention in the treatment program. ASI problem severity scores improved in problem areas where needed services were provided, with the exception of legal services. Improvement in drug use severity score was seen for two areas in which needed services were provided, childcare and housing.

3.2. Matching Based on Clients' Changing Status

In contrast to models targeting a pretreatment feature of the patient are those that regard key intervention variables as "moving targets" requiring repeated reassessment and tailoring of the intervention during the course of treatment. Adjusting the therapeutic approach dynamically makes intuitive sense, and many practitioners would agree with the statement of Hoyt and Miller (2000, p. 291) that "working with clients' stage of motivation, language, goals and theories of change often obviates or simply dissolves resistance." Or phrased more colorfully, "It is easier to ride a horse in the direction it's going" (Hoyt & Miller, p. 290).

3.2.1. Stages of Change Models. The transtheoretical model of change is well known to behavioral scientists. It describes an organizing framework for human behavioral change that has been applied to a wide range of addictive behaviors during the 20 years since it was first proposed by DiClemente and Prochaska. The model consists of three basic constructs: Individuals engaging in change are seen as (1) moving through five stages, (2) aided by 10 distinctive processes, (3) and needing to resolve multiple problem areas. Successful change is typically a cyclic rather than linear passage through the stages and requires performance of particular tasks to pass from one stage to another to attain and maintain change (DiClemente & Prochaska, 1998).

A large amount of clinical and experimental data exists on applications of the model to multiple phases of the treatment process, from recruitment to outcome, and across numerous addictive disorders. For example, probably the largest amount of data using the model is in the smoking area, in which stage matched interventions seem more helpful than simple standardized care. Relative to the theory's role in matching is the question whether stage membership is a useful predictor of outcome (Davidson, 1998). Although particular processes, it has been shown, match with stage status in cross-sectional data, it would be informative to have prospective data showing that particular processes or tasks facilitate the transition from one stage to another. In this review, we do not attempt to review the large body of data on stage models and will highlight only a few recent results illustrating how stage status and the use of processes may be useful variables for matching alcoholic clients to more effective treatments.

3.2.2. Project MATCH A Priori Hypotheses. In Project MATCH, it was postulated that subjects initially lower in motivation would do better in Motivational Enhancement Therapy, compared to Cognitive Behavioral Therapy. This did not occur during treatment or at 6- or 9-month follow-ups, but appeared only at the 12-month follow-up (Project MATCH Research Group, 1997a). The implications of this delayed effect are somewhat puzzling. Despite the lack of differential treatment effects early in treatment, it is noteworthy that overall, independent of treatment group, readiness to change was found as a strong predictor of drinking status through 1 year after the end of treatment.

3.2.3. Self-Efficacy and Goal Attainment. A recent study bears on the issue whether one can show prospectively that particular tasks facilitate the transition from one stage to another. Carbonari and DiClemente (2000) retrospectively examined Project MATCH data for pre- to posttreatment changes in stage and self-efficacy variables reflecting the transtheoretical model. The marker variables used were a set of behaviors and cognitive steps (goals) taken by the patient throughout the treatment period. The authors found that the greater the number of goals attained, the higher the likelihood that the client attained abstinence during the course of treatment. For example, clients who attained five goals during treatment were 15 times more likely to be abstinent than drinking heavily, whereas for clients attaining only one goal, the odds ratio was only 0.26. The authors suggest that characterizing progress in this way can assist therapists in planning phased treatment. In contrast, Herzog et al. (1997) using other data sources were unable to show that there were certain processes employed by problems drinkers who move from one stage to another, compared with those who do not show such movement.

3.2.4. Readiness, Importance, and Confidence. According to Rollnick (1998), three factors, readiness, importance, and confidence, are more sensitive criteria for matching and cut across treatments and environments. The clients' views of the importance of change, their willingness to undertake it at that time, and their confidence to achieve it are, potentially, the critical "triggers" of change. External environmental factors act through these triggers, and the job of treatment is to keep pace with the client's levels of these three ingredients. Thus, the therapist needs to track the patient's level of readiness, importance, and confidence and work with it. Rather than multiple strategies based on oversimplified models of single pretreatment characteristics, Rollnick envisions a single broad strategy, that is, an ongoing process wherein the therapist matches both the topic and style of the conversation to the shifting needs and readiness of the client to change.

3.2.5. Stepped Care Model. Another variant of the dynamic, or time varying, approach to treatment selection is that of Sobell and Sobell (1999) who object (p.337) to the practice wherein "clients are still offered only one treatment regardless of their histories or problem severity." They suggest adjusting

treatment to changes in critical client parameters throughout the course of treatment. They have proposed application of the Stepped Care Model, a fairly common approach to individualizing treatment in medical practice to treating alcoholism. The principle is first to assess and then use the least intensive intervention that has a reasonable chance of success with a particular patient. If this is unsuccessful, the sequence repeats, further assessment is performed, and a more intensive or alternative treatment is prescribed. The approach is seen as a dynamic and performance-based process, rather than a static event. More intensive (and expensive) treatments are reserved for the more severe cases and/or when lesser treatments fail. Sobell and Sobell emphasize that the treatments recommended should reflect current literature and standards of efficacy.

3.3. The Prescriptive Approach to Matching

Models from the treatment of mental health disorders, such as depression, have advocated what might be termed a fully prescriptive model. For example, Beutler and Martin (2000) criticize the myth of treatment simplicity wherein predictive matching is based only on an initial problem or symptoms. Treatment planning should take into account the "fit" of empirically verified therapies with important nondiagnostic information about the patient and the patient's environment, such as nature of the treatment relationship, features of the clinician, and needs. They advocate "individualization of interventions using empirically derived methods that cut across and integrate methods from different theoretical models of treatment" (p. 11). They applied methods of Systematic Treatment Selection to a variety of data sets to empirically derive and codify Prescriptive Therapy treatment manuals.

3.4. ASAM Patient Placement Criteria

The ASAM Patient Placement Criteria (PPC) are a set of guidelines used by clinicians to match patients to a level of care, as opposed to a particular treatment modality (Mee-Lee, 2001). They are based on objective clinical assessment of six dimensions of the patient's clinical status, functioning, and environment, which map by means of assignment algorithms onto a continuum of treatment levels. The full assessment includes screening for a problem, a diagnosis, and multidimensional assessment of the patient on readiness for treatment, relapse potential, and environmental risks. Table 2 shows the six dimensions of assessment and the five basic levels of care.

The ASAM guidelines call for substance abuse facilities to have policies and procedures to allow "unbundling," or separation, of clinical services from social services. This is an improvement over older models in which patients are assigned to fixed treatment programs, often based on narrow medical considerations. Application of the model is intended to be dynamic, progress is

Table 2. Outline of ASAM Assessment Dimensions and Treatment Levels

Assessment Dimensions (Problem Areas)	
Dimension 1:	Acute intoxication and/or withdrawal potential
Dimension 2:	Biomedical conditions and complications
Dimension 3:	Emotional, behavioral, or cognitive conditions and complications
Dimension 4:	Readiness to change
Dimension 5:	Relapse
Dimension 6:	Recovery environment
Treatment Levels (Levels of Care)	
Level 0.5:	Early intervention
Level I:	Outpatient services
Level II.1:	Intensive outpatient
II.2:	Partial hospitalization
Level III.1:	Clinically managed low-intensity residential treatment
III.3:	Clinically managed medium intensity residential treatment
III.5:	Clinically managed high intensity residential treatment
III.7:	Medically monitored intensive inpatient treatment
Level IV:	Medically managed intensive inpatient services

continually monitored, and adjustments are made in the level of ongoing care as indicated.

The ASAM criteria have been subjected to an orderly sequence of refinement and clinical testing summarized by Gastfriend and Mee-Lee (*in press*). Progressive refinements of the system have made it relevant to dually diagnosed patients, multiple needs in addition to addiction treatment, readiness to change, and adolescents. Practical problems have been addressed with computer-based administration and scoring mechanisms (Gastfriend, Lu, & Sharon, 2000).

Empirical data were initially lacking on the ability of the assignment rules to place patients accurately in the most appropriate level of care. A recent set of studies has begun to provide support for the predictive validity of the rules. Gastfriend et al. (*in press*) cite several studies supporting the PPC as a valid treatment-planning tool. Two naturalistic studies show encouraging results, one a Boston VA sample of 95 male veterans, the other sample of 258 in New York City. In the VA study, those who were classified by the ASAM algorithm as needing the more intense level of care (Level IV hospitalization) but who received only Level III (residential care) required nearly twice as many hospital bed days in the following year as the patients who received and were classified in need of Level II or Level III care. Similarly, in the New York sample, those who received a lower level of care than recommended by their score, based on ASAM criteria, had worse outcomes than patients who received the matched level of care.

To date, only one randomized, controlled, multisite clinical trial has been conducted, and analysis is now underway. Gastfriend and Mee-Lee have

reported a preliminary analysis of the 700 participants from several sites in Massachusetts (Gastfriend & Mee-Lee, in press). Those mismatched to a lower level of care than recommended by the guidelines showed poorer treatment engagement or slower improvement on several dimensions of addiction severity.

Gastfriend and Mee-Lee conclude that, taken together, the concurrent and predictive validity studies done to date support the PPC as clinically meaningful, feasible, and predictive enough to warrant further rigorous, large-scale evaluation. The ASAM Patient Placement criteria are now the most widely used clinically. As of 1999, at least 17 states formally adopted the criteria for clinician use, as have the VA and Department of Defense health care facilities.

4. Future Prospects for Research on Treatment Selection and Matching

4.1. Summary of Recent Trends

4.1.1. Single Characteristic Models. The previous sections have reviewed models and research results from the years since the publication of the Project MATCH results in 1997. The largest number of these reports was studies matching single patient characteristics to behavioral or pharmacological treatments. Consistent with Project MATCH's failure to confirm the benefits of differential treatments for either antisocial personality type or alcoholic subtype, two studies published in 2000, likewise, found no difference in outcome for these characteristics. Two of three studies on disorder severity and treatment intensity suggested that more severely disordered patients may benefit more from higher structure/more intense treatment.

Since 1996, 12 matching studies using pharmacological agents were published, a total of nine found differential treatment effects. Both positive and negative results have been reported for alcoholics with comorbid conditions such as depression and anxiety. In addition, initial studies have suggested differential effects of pharmacological agents for Type A and B alcoholics. Although intriguing and intuitively appealing, further replication is clearly needed before these matches can be considered prescriptive. Ongoing basic research on the basic biological mechanisms of alcohol drinking behavior and data on the neuropharmacological actions and clinical effects of new agents from studies such as the multisite clinical trial COMBINE (COMBINE Research Group, in press) will also be informative.

4.1.1.1. Conceptual Implications. The research of the 1990s on matching to behavioral therapies has produced an additional benefit for the field, that is, codification of new standards for treatment research studies. One such effort is the work of Moyer, Finney, Elworth, and Kraemer (2001) that reviewed 55 published studies of interactions. One methodological conclusion was that the potential for Type 1 error in most matching studies has been high due to undersized samples and the large number of statistical tests performed. They found

that only about 33% of the studies examined had a "reasonable probability" of finding a medium size matching effect. To maximize the chances for detecting matches where they exist, the authors recommend that future studies carefully estimate and then use the proper sample size, employ treatments that are sufficiently distinct from one another to allow contrasts to emerge, and focus on patients at the extremes of the distributions of the matching characteristics.

The single characteristic matching model assumes that the patient feature of interest exerts such a strong influence that matching to treatment based on this one feature will dominate outcome over and above other influential factors. It also assumes that there is sufficient knowledge of the mediators and moderators of treatment effects to generate reasonably informed hypotheses linking one specific treatment with a particular characteristic. Longabaugh and Wirtz (2001) published an extensive examination of the testing of the causal chains postulated as underlying the MATCH hypotheses. They concluded that there is not sufficient knowledge of the way the Project MATCH treatments exert their effects, and, furthermore that the methodological requirements for formulating and testing such hypotheses are not as straightforward as once assumed. They propose conceptual and statistical approaches to formulate and test moderator and mediator relationships. Systematic application of these refined approaches in future studies may enhance our interpretation of treatment research results. In fact, it would be useful for designers of all trials that test the efficacy of an intervention to routinely consider incorporating tests of proposed causal chains in their protocols.

4.1.2. Multidimensional Models. A number of authors have argued that matching on the basis of a single pretreatment characteristic is oversimplified. Factors proposed to mitigate against single element models include the changing nature of the client's readiness for change; the influence of the context (e.g., the client's situation and the treatment setting); and the constraints of the treatment delivery system, such as the need to reserve the more extensive (and expensive) treatments for the most severe cases.

However, few systematic approaches to the application of multidimensional approaches to treatment selection have been proposed, although general principles have been suggested. For example, Sobell suggests an approach based on the medical Stepped Care Model, and Rollnick recommends that therapists match their approach to the client's changing readiness level as the therapy progresses in real time. Breslin et al. (2000) proposed formulating decision trees based on practitioners' experience so that the way clinicians make decisions among alternative treatments can be analyzed. This documentation may be useful to understand what actually happens at the clinical level and to identify contextual factors, real life constraints, and other factors that may not be captured by normative methods using a priori selected domains. Breslin et al. described a procedure to code interviews and identify key decision factors, for example, consequences of use, use pattern, coping skills, and scores on the Alcohol Dependence Scale/Drug Abuse Screening Test (ADS/DAST).

The ASAM Patient Placement Criteria (PPC) appear to offer a more systematic and objective approach to blending a manageable range of pertinent features: withdrawal potential; medical factors; emotional, behavioral, and cognitive conditions; readiness to change; relapse potential; and recovery environment. Early validation efforts have been encouraging, but additional randomized evaluations with adequate follow-up rates are also needed. The developers hope that, as more evidence accumulates on the ASAM derived placement criteria, a national data network will be built to serve as a system of feedback and refinement.

4.2. Future Prospects

Does matching represent a viable avenue to improve treatment selection? On one hand, the optimist may intuitively feel that matching *must* exist, at least to some degree, because we observe that particular treatments work quite well for some patients, but not for others. Thus, for some of those treated, the therapy is "just right"—a good match—and produces a favorable outcome. The challenge lies in discovering what is different about the clients for whom the treatment works and those for whom it fails. With advances in methods to dissect treatment components and test the mechanisms of action of therapies, this is a daunting, but perhaps not impossible task.

Another view is more pessimistic. An analogy is the dilemma depicted by an ancient fable from India in which several blind men are attempting to identify an unknown animal (actually an elephant) by each feeling different parts of the large and mysterious creature. As they compare their descriptions of the trunk, the tail, and the foot, they are thrown into confusion by their disparate impressions and can draw no conclusions about the beast that they are examining. In a similar vein, the huge array of possible interactions between client and treatment is all but overwhelming, and the failure of Project MATCH to replicate promising matches has discouraged many in the field from pursuing matching research.

Unfortunately, the degree of specificity for treatment selection that will be attainable in the future is unknown now. However, from a review of the recent literature, it seems fair to predict that the "fit" between client and treatment can only become better as research continues. The field is progressing from simplistic to more sophisticated matching models that are more flexible, varied, and able to test and integrate single characteristic matches. In addition, some matching models now incorporate key generic factors, such as the role of motivation, the influence of context, and the changing patient profile over time. Identification of new pharmacological agents used in combination with behavioral therapies and increased knowledge of genes underlying alcohol drinking behavior can further increase specificity. Assuming that our expectations are reasonable for the amount of improvement that matching may afford and that multidimensional strategies are emphasized, it is likely that we will see improved client-treatment "fits" emerge.

References

- Allen, J.P., & Kadden, R.M. (1995). Matching clients to alcohol treatments. In R.K. Hester, & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches. Effective Alternatives*. Boston: Allyn and Bacon.
- Babor, T. (ed.) (1999). Comments on Project MATCH: Matching alcohol treatments to client heterogeneity. *Addiction* 94(1), 31–69.
- Ball, S.A., Jaffe, A.J., Crouse-Artus, M.S., Rounsville, B.J., & O'Malley, S.S. (2000). Multidimensional subtypes and treatment outcome in first-time DWI offenders. *Addictive Behaviors* 25, 167–181.
- Beutler, L.E., & Martin, B.R. (2000). Prescribing therapeutic interventions through strategic treatment selection. *Cognitive and Behavioral Practice* 7, 1–17.
- Breslin, F.C., Gladwin, C.H., Borsoi, D., & Cunningham, J.A. (2000). Defacto client-treatment matching: How clinicians make referrals to outpatient treatments for substance use. *Evaluation and Program Planning* 23, 281–291.
- Carbonari, J.P., & DiClemente, C.C. (2000). Using transtheoretical model profiles to differentiate levels of alcohol abstinence success. *Journal of Consulting and Clinical Psychology* 68, 810–817.
- COMBINE Research group, (in press). Testing combined pharmacotherapies and behavioral interventions in alcohol dependence.
- Conrod, P.J., Stewart, S.H., Pihl, R.O., Cote, S., Fontaine, V., & Dongier, M. (2000). Efficacy of brief coping skills interventions that match different personality profiles of female substance abusers. *Psychology of Addictive Behaviors* 14, 231–242.
- Cornelius, J.R., Salloum, I.M., Haskett, R.F., Daley, D.C., Cornelius, M.D., Thase, M.E., & Perel, J.M. (2000). Fluoxetine versus placebo in depressed alcoholics: A 1-year follow-up study. *Addictive Behaviors* 25, 307–310.
- Cornelius, J.R., Salloum, I.M., Ehler, J.G., Jarrett, P.J., Cornelius, M.D., Perel, J.M., Thase, M.E., & Black, A. (1997). Fluoxetine in depressed alcoholics: A double blind, placebo-controlled trial. *Archives of General Psychiatry* 54, 700–705.
- Davidson, R. (1998). The Transtheoretical model: A critical overview. In W.R. Miller & N. Heather (eds.), *Treating Addictive Behaviors*, 2nd ed. New York: Plenum Press, pp. 25–38.
- DiClemente, C., & Prochaska, J.O. (1998). Transtheoretical model of change: Stages of change and addictive behaviors. In W.R. Miller & N. Heather (eds.), *Treating Addictive Behaviors*, 2nd ed. New York: Plenum Press, pp. 1–24.
- Gastfriend, D.R., & Mee-Lee, D. (in press). The ASAM patient placement criteria: Context, concepts and continuing development. *Journal of Addictive Diseases*.
- Gastfriend, D.R., Lu S.H., & Sharon, E. (2000). Placement matching: Challenges and technical progress. *Substance Use and Misuse* 35, 2191–2213.
- Herzog, T.A., Abrams, D.B., Emmons, K.M., Linnan, L., & Shadel, W. (1997). *Do Processes of Change Predict Stage Movements?* San Francisco: Society of Behavioural Medicine.
- Hoyt, M.F., & Miller, S.D. (2000). Stage-appropriate change-oriented brief therapy strategies. In J. Carlson & L. Sperry (eds.), *Brief Therapy with Individuals and Couples*. Phoenix, AZ: Zeig, Tucker & Theisen, pp. 289–330.
- Hser, Y.-L., Polinsky, M.L., Maglione, M. & Anglin, M.D. (1999). Matching clients' needs with drug treatment services. *Journal of Substance Abuse Treatment* 16, 299–305.
- Jaffe, A.J., Rounsville, B., Chang, G., Schottenfeld, R.S., Meyer, R.E., & O'Malley, S.S. (1996). Naltrexone, relapse prevention, and supportive therapy with alcoholics: An analysis of patient treatment matching. *Journal of Consulting and Clinical Psychology* 64, 1044–1053.
- Johnson, B.A., Ait-Daoud, N., & Prihoda, T.J. (2000). Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: From hypotheses to preliminary clinical evidence. *Alcoholism: Clinical and Experimental Research* 24, 737–742.
- Johnson, B.A., Roache, J.D., Javors, M.A., DiClemente, C.C., Cloninger, C.R., Prihoda, T.J., Bordnick, P.S., Ait-Daoud, N., & Hensler, J. (2000). Odansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *Journal of American Medical Association* 284, 963–971.

- Kadden, R.M., Litt, M.D., Cooney, N.L., Kabela, E., & Getter H. Prospective matching of alcoholic clients to cognitive-behavioral or interactional group therapy. *Journal of Alcohol Studies* 62, 359–369.
- Kalman, D., Longabaugh, R., Clifford, P.R., Beattie, M., & Maisto, S.A. (2000). Matching alcoholics to treatment: Failure to replicate finding of an earlier study. *Journal of Substance Abuse Treatment* 19, 183–187.
- Karno, M.P., Beutler, L.E., & Harwood, M. (2002). Interactions between psychotherapy procedures and patient attributes that predict alcohol treatment effectiveness: A preliminary report. *Addictive Behaviors*, 27, 779–797.
- Kranzler H.R. (2000). Pharmacology of alcoholism: Gaps in knowledge and opportunities for research. *Alcohol & Alcoholism* 35, 537–547.
- Kranzler, H.R., Burleson, J.A., DelBoca, F.K., Karner, Brown, & Bohn (1994). Buspirone treatment of anxious alcoholics: A placebo-controlled trial. *Archives of General Psychiatry* 51, 720–31.
- Kranzler, H.R., Burleson, J.A., Brown, J., & Babor, T.F. (1996). Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcoholism: Clinical and Experimental Research* 20, 1534–1541.
- Litten, R.Z., & Allen, J.P. (1998). Advances in development of medications for alcoholism treatment. *Psychopharmacology* 139, 20–33.
- Longabaugh, R. and Wirtz P. (2001). *Project MATCH Hypotheses: Results and Causal Chain Analyses*, Project MATCH Monograph Series, Vol. 8. DHHS.
- Longabaugh R., Wirtz, P., Zweben, P.W., & Stout, R.L. (1998). Network support for drinking, Alcoholics Anonymous and long-term matching effects. *Addiction* 93, 1313–1333.
- Malcom, R., Anton, R.F., Randall, C.L., Johnson, A., Brady, K., & Thevos, A. (1992). A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcoholism: Clinical and Experimental Research* 16, 1007–1013.
- Mason, B.J., Kocsis, J.H., Ritvo, E.C., & Cutler, R.B. (1996). A double-blind placebo-controlled trial of desipramine in primary alcoholics stratified on the presence or absence of major depression. *JAMA*, 275, 1–7.
- Mattson, M.E., Allen, J.P., Longabaugh, R., Nickless, C., Connors, G.J., & Kadden, R.M. (1994). Chronology of empirical literature matching clients to alcoholism treatments. In D. Donovan and M.E. Mattson (eds.), *Alcoholism Treatment Matching Research: Methodologic and Clinical Approaches*, *Journal Studies on Alcohol Supplement No. 12*, 16–29.
- Mattson, M.E. (1998). Finding the right approach. In W.R. Miller & N. Heather (eds.). *Treating Addictive Behaviors*, 2nd ed. New York: Plenum Press, pp. 163–172.
- McGrath, P.J., Nunes, E.V., & Stewart, J.W. (1996). Imipramine treatment of alcoholics with major depression: A placebo-controlled clinical trial. *Archives General Psychiatry* 53, 232–240.
- McGee, M.D., & Mee-Lee, D. (1997). Rethinking patient placement: The human service matrix model for matching services to needs. *Journal of Substance Abuse Treatment* 14, 141–148.
- McLellan, A.T., Grissom, G.R., Zanis, D., Randall, M., Brill, P., & O'Brien, C.P. (1997). Problem-service 'matching' in addiction treatment. A prospective study in 4 programs. *Archives of General Psychiatry* 54, 691–694.
- McLellan, A.T., & McKay, J.R. (1998). Components of successful treatment programs: Lessons from the literature. In A.W. Graham & T.K. Schultz (eds.), *Principles of Addiction Medicine*. Chevy Chase, MD: American Society of Addiction Medicine, pp. 327–343.
- Mee-Lee, D. (2001). *ASAM Patient Placement Criteria for the Treatment of Substance-Related Disorders*. Chevy Chase, MD: American Society of Addiction Medicine.
- Moyer, A., Finney, J.W., Elworth, J.T., & Kraemer, H.C. (2000). Can methodological features account for patient-treatment finding in the alcohol field? *Journal of Studies on Alcohol* 62–73.
- Nielsen, B., Nielsen, A.S., & Wraae, O. (1998). Patient-treatment matching improves compliance of alcoholics in outpatient treatment. *Journal of Nervous & Mental Disease* 186, 752–760.
- Pettinati, H.M., Volpicelli, J.R., Kranzler, H.R., Luck, G., Rukstalis, M.R., & Cnaan, A. (2001). Double blind clinical trial of sertraline treatment for alcohol dependence. *Journal of Clinical Psychopharmacology* 21, 143–153.
- Pettinati, H.M., Volpicelli, J.R., Kranzler, H.R., Luck, G., Rukstalis, M.R., & Cnaan, A. (2000). Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcoholism: Clinical and Experimental Research* 24, 1041–1049.

- Prochaska, J.O., & Diclemente, C.C. (1998). Comments, criteria, and creating better models. In W.R. Miller & N. Heather (eds.), *Treating Addictive Behaviors*, 2nd ed. New York: Plenum Press, pp. 39–45.
- Project MATCH Research Group. (1993). Project MATCH: Rationale and methods for a multisite clinical trial matching patients to alcoholism treatment. *Alcohol: Clinical and Experimental Research* 17(6), 1130–1145.
- Project MATCH Research Group. (1998a). Clinical implications from Project MATCH. *Journal of Mental Health* 7(6), 589–602.
- Project MATCH Research Group. (1997a). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58(1), 7–29.
- Project MATCH Research Group. (1997b). Project MATCH secondary a priori hypotheses. *Addictions* 92(12), 1671–1698.
- Project MATCH Research Group. (1998b). Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcoholism: Clinical and Experimental Research* 22, 1300–11.
- Rollnick, S. (1998). Readiness, importance, and confidence: Critical conditions of change in treatment. In W.R. Miller & N. Heather (eds.), *Treating Addictive Behaviors*, 2nd ed. New York: Plenum Press, pp. 49–60.
- Rychtarik, R.G., Connors, G.J., Whitney, R.B., McGillicuddy, N.B., Fitterling, J.M., & Wirtz, P.W. (2000). Treatment settings for persons with alcoholism: Evidence of matching clients to inpatient versus outpatient care. *Journal of Consulting and Clinical Psychology* 68, 277–289.
- Sobell, M.B., & Sobell, L.C. (1999). Stepped care for alcohol problems: An efficient method for planning and delivering clinical services. In J.A. Tucker, D.M. Donovan, & G.A. Marlatt (eds.), *Changing addictive behavior: Bridging Clinical and Public Health Strategies*. New York: Guilford, p. 331.
- Thornton, C.C., Gottheil, E., Weinstein, S.P., & Kerachsky, R.S. (1998). Patient-treatment matching in substance abuse: Drug addiction severity. *Journal of Substance Abuse Treatment* 15, 505–511.
- Trent, L.K. (1998). Evaluation of a four- versus six-week length of stay in the Navy's alcohol treatment programs. *Journal of Studies on Alcohol* 270–279.

Psychotherapy and Motivational Enhancement

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1. Introduction

Psychotherapy as a treatment for alcohol abuse and dependence has had a conflicted historical relationship. Early in the history of psychoanalytic treatments, analytic procedures were deemed appropriate to resolve the unconscious causes of drinking once an individual had stopped drinking but seemed to do little to stop the actual drinking behavior. With the rise of Alcoholics Anonymous (AA) and the advent of the behaviorists' focus on drinking behavior, the value of traditional psychotherapy was seriously questioned, resulting in a reluctance to prescribe any type of insight-oriented psychotherapy prior to a stable period of sobriety. Behavioral and cognitive/behavioral treatments, self-help groups, and pharmacological interventions became the primary focus of treatment during that time. In the past 15 or so years, there has been a resurgence of interest in psychotherapies and psychosocial treatments that are not predominantly behavioral. A renewed and radically different focus on cognition and motivation has spurred this resurgence. This review will examine recent controlled studies in the area of nonbehavioral psychosocial treatments. In addition to updating information on psychoanalytic and interpersonal approaches, this review will examine cognitive therapy and motivational enhancement treatments. Although there is much written about each of these approaches, this review will focus primarily on controlled studies or comparison studies that appeared in the literature in the past 10–15 years and will highlight promising areas for future research.

Of necessity, there will be some overlap and hopefully helpful redundancy with several other chapters in this volume. Many current treatment approaches to alcohol abuse and dependence are often pragmatically eclectic and do not adhere to a single theory. For example, there is often a blending of cognitive/behavioral approaches and the more purely cognitive treatments. Brief interventions that screen and intervene in settings that are non-traditional often include motivational interviewing types of interventions. At times, even interventions that focus on social systems, community networks, and social support include motivational enhancement procedures or techniques. This review will concentrate on studies of treatments that are conceptually clearer in orientation and clinically focused in application.

2. Psychodynamic Treatments

There are few controlled clinical trials of psychodynamic treatments compared with no-treatment controls or alternative alcoholism treatments. The majority of the outcome studies involving psychodynamic approaches for treating of alcohol abuse and dependence were conducted in the late 1960s and 1970s. Roth and Fonagy (1996) concluded in their review of these earlier studies that dynamic psychotherapy demonstrated positive results compared to no-treatment controls, as in the Kissin and colleagues (1970) study. However, when compared with minimal intervention strategies, psychodynamic treatments showed little additional benefit over these more minimal interventions, as demonstrated in Zimberg (1974) and Crumbach and Carr (1979). Additionally, they reported that one comparison of insight-oriented therapy with an occupational/recreational therapy control found that the control improved somewhat more than the insight-oriented group (Levinson & Sereny, 1969). In their summary of this review, Roth and Fonagy concluded that, compared to other alcohol treatments, psychodynamic therapy has a very high cost and little or no evidence of unique effectiveness.

There is one recent study published in 1992 by Ojeihagen and colleagues that compared long-term outpatient treatment for alcoholics randomly assigned to either psychiatric treatment (PT) based on psychodynamic principles or multimodal behavioral therapy (MBT), a cognitive-behavioral treatment. Treatments were designed to be either 1 or 2 years in duration. Of the 129 participants approached, 79 (61%) accepted randomization and were assigned either to PT for 1 or for 2 years or to MBT for 1 or 2 years. Attrition rates were substantial but were not significantly different between the two treatments. Of those assigned to PT, 25% of those assigned to 1 year dropped out compared to 38% randomized to 2 years. For those assigned to MBT, 29% of the 1-year group dropped out, compared to 50% of those assigned to 2 years. No significant differences between treatments were found for attrition rates or drinking outcomes. At follow-up, drinking outcomes were assessed using the number of misuse days (consuming more than four drinks during continuous

drinking and more than six on occasional drinking days) and not abstinence. The authors designated a maximum of 14 misuse days during a 1-year follow-up period as a favorable outcome. Favorable outcomes were reported for 40–44% during the third year of follow-up and did not differ by type or length of treatment. Although statistical power was minimal with such a small number of participants, this study produced inconclusive results for the benefits of longer treatments and no support for any unique effectiveness for either type of treatment. In general, there is little support for the utility of psychodynamically oriented treatments specifically for alcohol dependence or abuse.

3. Interpersonal Psychotherapy

A type of treatment that is related to the psychodynamic orientation is interpersonal or interactional psychotherapy. This treatment encourages participants to explore interpersonal relationships and problems through self-reflection, expression of emotions, and examination of current interactions within the treatment context. Although individual treatment options using this approach exist, most often, interpersonal, interactive treatment is delivered in group therapy. Interpersonal psychotherapy has received support in terms of its efficacy for a number of nonsubstance abuse disorders (e.g., depression). However, there has been little empirical support for the unique effectiveness of interpersonal therapy with substance abusers in several previous trials (Rounsaville & Carroll, 1993) including a version called supportive, expressive therapy employed in a large scale collaborative trial on the treatment of cocaine (Crits-Christoph et al., 1999).

Using an approach that is very similar to the interpersonal, supportive, expressive type of treatment, Matano and Yalom (1991) adapted interactive group therapy for chemically dependent individuals. The two primary foci of this treatment are the interpersonal relationships within the group in the here and now and conceptualizing the group as a social microcosm (see also Levy, 1997). The authors offer five basic principles or guidelines for clinicians who wish to integrate interactional group therapy with traditional chemical dependency approaches: (1) priority of recovery, (2) identification as an alcoholic/addict, (3) careful modulation of anxiety levels, (4) a therapeutic approach to responsibility, and (5) modification of the group process to incorporate into therapy the language and belief systems of Alcoholics Anonymous (Matano & Yalom, 1991, p. 273).

Empirical controlled studies investigating interactional group therapy are few in number. Controlled trials are difficult to accomplish because the size and makeup of the groups complicate analysis of results. The effectiveness of interactional group therapy with substance abusers has been tested mainly in treatment matching studies. Kadden, Cooney, Getter, and Litt (1989) compared outcomes for 96 male and female alcoholics randomly assigned to coping skills training versus interactional group psychotherapy. Participants were recruited

from a 21-day inpatient substance abuse treatment unit. Treatments under study were implemented postdischarge as aftercare. Matching variables included level of sociopathy, psychopathology, and neuropsychological impairment. At posttreatment, coping skills training was more effective for individuals with higher levels of sociopathy or psychopathology. Participants, who had lower levels of sociopathy, had better outcomes in the interactional group therapy. Both coping skills and interactional group treatments had equivalent outcomes for subjects lower in psychopathology. Participants, however, with more neuropsychological impairment had better outcomes in interactional therapy. Cooney, Kadden, Litt, and Getter (1991) reported on 2-year follow-up results for these participants and found that the pattern of results described above was maintained. Although there were no significant differences between the two treatments in terms of a main effect of treatment, participants with less sociopathy and more neuropsychological impairment did significantly better in interactional group therapy.

Using data collected from the study described above, Litt and colleagues (1992) compared coping skills versus interactional group psychotherapy in 79 male alcoholics classified as either Type A or Type B. A late onset, few vulnerability markers, less psychiatric comorbidity, fewer alcohol-related problems, and a good prognosis characterize Type A alcoholics. Those labeled Type B have early onset, rapid progression, familial vulnerability, comorbid psychiatric disturbance, more severe alcohol-related problems, and a poor prognosis. Type A alcoholics with less pathology and problems had better outcomes in interactional group than in coping skills treatment. On the other hand, those classified as Type B fared better in coping skills treatment than in interactional group therapy.

To date, research results from studies examining both alcohol and substance abuse treatment settings do not support a unique role for interactional group therapy in the treatment of alcohol-dependent and abusing patients. However, there is some evidence indicating that this type of treatment may be more effective for some types of clients. Although the matching hypothesis has not fared well for similar types of comparisons in large-scale studies (Project MATCH Research Group, 1997a, b), there was not a direct replication of the Kadden and colleagues studies. Additional research could explore the relationship of interactional group therapy with Type A and B patients and those with sociopathy. Moreover, this type of treatment could be used in conjunction with psychopharmacological interventions to evaluate its unique contribution in promoting maintenance and preventing relapse for specific subgroups of clients with alcohol problems.

4. Cognitive Therapy

There are several types of cognitive therapies for alcohol and substance abuse problems described in the literature. Albert Ellis and colleagues described

a version of Rational Emotive Therapy (RET) that was adapted for treating alcohol abuse and dependence (Ellis, McInerney, & DiGiuseppe, 1988). This approach is similar to the standard RET approach that examines beliefs about drinking and drinking-related expectancies, then challenges those beliefs, and assists the client to create realistic and healthy beliefs, as well as engage in more adaptive self-talk. Although this approach is popular and many therapists have been trained in the specifics of RET, no controlled studies of the therapy with alcohol-dependent or abusing patients have been conducted in recent years.

Beck, Wright, Newman, and Liese (1993) describe another type of treatment that is cognitive and based on the more general cognitive therapy for psychological problems developed by Beck in 1976. This approach is collaborative, active, and structured. The cognitive model assumes that dysfunctional beliefs regarding the use of alcohol (e.g., "I can't be happy unless I drink"), the anticipated negative withdrawal syndrome, and believing that craving is beyond the individual's control all contribute to maintaining use. Therefore, treatment focuses on assessing situations in which the client is likely to drink and altering faulty beliefs about alcohol. Traditional cognitive techniques such as the Socratic method and homework assignments are used. In addition, skills for managing cravings, coping with stress, and assertiveness are often included as components of treatment, making it more of a cognitive/behavioral type of therapy. Beck and his colleagues (1993) also describe what are more traditional behavioral techniques, including activity scheduling, behavioral rehearsal, and relaxation training that are used in conjunction with the more purely cognitive ones.

Few empirical studies have examined this type of cognitive therapy for treating alcohol abuse and dependence. In a quasi-experimental study, Whorley (1996) examined the effectiveness of two cognitive techniques for increasing patient involvement with continuing care/aftercare program resources and agencies for inpatient substance abusers. This study used a historical control group. Cognitive techniques were implemented in a group setting and included analysis of advantages and disadvantages and problem-solving activities. The first technique examined participant beliefs regarding the relative benefits and costs of attending aftercare treatment. Problem-solving skill training required participants to identify potential barriers to attending aftercare treatment. Results indicated that patients who received cognitive therapy had significantly greater acceptance of and initial contact with aftercare agencies than subjects who did not receive cognitive therapy. Use of the historical control comparison condition and the fact that these techniques were added to a more comprehensive treatment make conclusions difficult and implications limited.

The absence of controlled studies of cognitive techniques clearly distinguished from cognitive behavioral techniques (reviewed by Kadden in this volume) make it difficult to evaluate the unique effectiveness of cognitive therapy. Cognitive-behavioral treatment of substance abusers is more common and better established (Carroll, 1999; Carroll & Schottenfeld, 1997). Although it may be

difficult to distinguish cognitive components, additional research is needed to investigate the effectiveness and timing of cognitive techniques apart from a more integrated cognitive-behavioral treatment for alcohol-dependent and abusing populations. There does appear to be consensus that problematic cognitions play a role in recovery and relapse and include expectancies, cognitive dimensions of craving, and the problematic rationalizations labeled "stinking thinking" at AA meetings (Quigley & Marlatt, 1999). Cognitive therapy approaches that directly address these problematic beliefs and thoughts could logically be expected to play an important part in supporting a sustained change in drinking behavior. However, details about the scope, efficacy, and timing of these cognitive interventions are not established and would benefit from additional controlled research.

5. Motivational Enhancement Intervention

5.1. *Historical Foundations*

Early research into motivational approaches for alcohol problems focused mainly on problem drinkers. More than 20 years ago, William R. Miller and colleagues developed an intervention called the Drinker Check-Up (DCU) to influence problem drinkers to change drinking behavior. The DCU included an assessment using a battery of measures sensitive to alcohol's early effects on health and behavior. Results were given as feedback and used to increase treatment seeking and suppress alcohol consumption (Miller, Sovereign, & Krege, 1988).

Motivational interventions were offered in the context of this feedback and evaluated in a series of four controlled trials that originally included problem drinkers and excluded dependent drinkers. In the first study, problem drinkers were randomized to receive an immediate or delayed Drinker Check-up (Miller, Sovereign, & Krege, 1988). The immediate group showed significantly greater reduction in drinking compared with the waiting list control. When the wait-list control group was offered the DCU intervention, they also demonstrated comparably favorable outcomes. Miller, Benefield, and Tonigan (1993) replicated these results in a study that examined the impact of counselor style in changing problem drinking. Problem drinkers ($n = 42$; 18 women and 24 men) were randomized into three groups: (1) immediate checkup with directive-confrontational counseling, (2) immediate checkup with client-centered counseling, and (3) delayed checkup (wait-list control). The Drinker Check-up consisted of a 2-hour motivational interview based on an intensive measurement of alcohol-related risks and impairment obtained in an evaluation session. Overall, the intervention produced a 57% reduction in drinking within 6 weeks, which was maintained at 1 year. Clients who received an immediate checkup showed a significant reduction in drinking relative to controls. The directive-confrontational style, however, yielded more resistance from clients and predicted a poorer outcome at 1 year.

Focusing on a more clinical sample, Bien, Miller, and Boroughs (1993) applied this approach to more severe dependent drinkers from a VA outpatient substance abuse program ($n = 32$). They found that brief motivational interviewing (2 additional hours of assessment and a 1-hour motivational interview) was superior to standard treatment (an attention-placebo interview) on a composite variable that consisted of total standard drinks, peak blood alcohol level (BAL), and percentage days abstinent obtained at a 3-month follow-up. By 6-month follow-up, the superiority of the treatment was modest and no longer significant.

The fourth study investigated DCU or motivational interviewing as a strategy to prepare patients for residential alcoholism treatment (Brown & Miller, 1993). Consecutive admissions were alternately assigned either to receive or not receive a 2-hour motivational assessment and interview in addition to standard care procedures. Results indicated that patients who received the motivational interview participated more fully in treatment (as evidenced by therapist ratings) and showed significantly less alcohol consumption at a 3-month follow-up. The effects of motivational interviewing were mediated by increased participation in the treatment. These studies demonstrated a potentially important role for assessment, feedback, and motivational enhancement in interventions with alcohol problems of differing levels of intensity and across a range of severity.

5.2. Motivational Interviewing and the Stages of Change

Motivational Interviewing (MI) represents a more general and practical approach aimed at changing addictive and other health behaviors based on principles of motivational psychology, client-centered therapy, and the stages of change model (Miller & Rollnick, 1991). MI focuses on enhancing and facilitating the client's own internally motivated change process. Responsibility for changing addictive behavior, it is assumed, lies within the client, and ambivalence is recognized as a natural part of this change process. MI is designed to assist clients in working through ambivalence and in moving toward change. The MI therapist uses techniques such as personalized feedback, reflective listening, exploring the pros and cons of change, supporting client self-efficacy, and eliciting self-motivational statements such as problem recognition and concern. Notably, MI emphasizes the client's personal choice regarding change, deemphasizes diagnostic labels, and avoids arguing with and confronting the client.

The Stages of Change and the Transtheoretical Model developed by Prochaska and DiClemente provided a conceptual foundation and practical tools for evaluating motivation for change (DiClemente & Prochaska, 1998; DiClemente, 1999; Yahne & Miller, 1999). The stages of change segmented the process of changing problem behaviors like alcohol addiction into a series of five stages beginning with precontemplation and ending with maintenance. Motivational interventions were viewed as particularly relevant for individuals

in the early stages of change. In particular, MI strategies were especially tailored for individuals who were in precontemplation and reluctant to change, struggling with the ambivalence of contemplation, or needing to develop a personally relevant change plan in preparation for making a change in drinking (DiClemente, 1999). Individuals coming into alcoholism and substance abuse treatment in various stages of change have been identified in both outpatient and inpatient settings (DiClemente & Hughes, 1990; Isenhart, 1994). As interventions and treatments became more proactive reaching out to various nontreatment settings and individuals became mandated to treatment with regularity, there was more and more emphasis on motivation and the need to address individuals in early stages of change (DiClemente, Bellino, & Neavins, 1999).

5.3. Current Status of Motivational Enhancement Interventions

Adaptations of Motivational Enhancement types of interventions have ranged from very brief (5 to 15 minutes) office interventions to single session interviews. This review will concentrate on studies that include more clinical populations since this volume includes a review of brief interventions that are often used in screening, intervention and referral studies in non-treatment-seeking populations (See Fleming chapter). Studies during the past 10 years have demonstrated that motivational interventions are moderately successful in initiating change among a variety of alcohol abusing and alcohol-dependent individuals. For example, Heather, Rollnick, Bell, and Richmond (1996) evaluated brief motivational interviewing (BMI) compared to skills based counseling (SBC) and a routine hospital control group in a study of heavy male drinkers on an inpatient hospital ward. Blinded 6-month follow-up interviews of 123 patients examined self-report and collateral sources of information on drinking. Although patients who received BMI or SBC showed greater mean reduction in a quantity-frequency measure of weekly alcohol consumption than controls, there were no significant differences in outcomes between the BMI and SBC groups. However, BMI was determined to be more effective than SBC among those patients assessed as in the precontemplation stage of change and deemed not ready to change.

There have also been a number of small pilot studies with individuals who range from minimally to more severely problematic drinkers. A study of Motivational Interviewing with pregnant alcohol drinkers demonstrated that a 1-hour motivational interviewing session was more effective than written information about the risks of drinking during pregnancy with 42 pregnant women from the University of New Mexico Medical Center obstetric clinics. Patients were stratified on drinking severity and randomized to receive either a 1-hour motivational interview that included feedback and potential impact on the fetus or a control informational letter from their health care provider about the risks of alcohol use in pregnancy. At the end of a 2-month follow-up, group differences were found in drinks consumed and drinking days and

reduction of blood alcohol concentration (BAC) levels; MI subjects fared better than controls (Handmaker, Miller, & Manicke, 1999).

Another recent case series analysis reported on 9 of 12 inpatients who screened positive for alcoholism after traumatic brain injury. This group received motivational interviewing and was compared with 20 historical untreated controls at 1-year follow-up. Seventy-six percent were male and they had an average age of 35 years. Eighty-nine percent of MI subjects and 55% of controls reported no alcohol during a typical week after discharge. These authors concluded that MI is feasible during inpatient rehabilitation and may reduce drinking after traumatic brain injury (Bombardier & Rimmele, 1999).

In a controlled trial of motivational enhancement therapy for mild to moderate dependent drinkers, Sellman and colleagues (2001) randomized 122 participants into three groups. After screening, participants were given either a four-session MET intervention or one of two control conditions: a four-session nondirective listening (NDRL) intervention or a single feedback/education session with no further counseling (NFC). MET was more effective than either of the two other conditions in reducing the percentage of individuals who reported heavy drinking (42.9% versus 62.5% for NDRL and 65% for NFC). This trial demonstrates that it is not simply time listening that is the active ingredient of MET. Similar outcomes of significantly reduced drinking were obtained in a recent clinical trial of a 6-week motivational intervention with maritally distressed women (Kelly, Halford, & Young, 2000).

Several other randomized trials examined motivational intervention in emergency departments of trauma centers that screened individuals with a wide range of drinking behaviors, including abuse and dependence. Overall, these trials, two with adults (Gentilello et al., 1999; Longabaugh et al., 2001) and one with adolescents (Monti et al., 1999) supported the efficacy of motivational enhancement interventions. These interventions in emergency settings demonstrated important clinical outcomes in terms of risk-taking, negative consequences of drinking, and some reduction in drinking. However, they did not always produce drinking reductions that differed significantly from control conditions, may not have been as effective with the most dependent of participants, and may need a booster session postdischarge to be most effective. Moreover, the number of participants who were not screened, refused, discharged early, or who were ineligible for some reason was large in some studies. Nevertheless, motivational interventions delivered to patients in emergency settings and compared to standard or minimal interventions appeared to benefit patients on relevant outcomes. Although considered minimal interventions, they often take up to an hour or more since they include, of necessity, an assessment of drinking behavior and a follow-up and are often much more than ordinarily occurs in the emergency setting for problematic drinkers.

Motivational enhancement interventions have not fared as well in other studies. For example, Kuchipudi, Hoben, Flickenger, and Iber (1990) randomly assigned 114 consecutive alcohol-drinking patients, who entered a medical service center with serious medical consequences of ulcer, cirrhosis, or pancreatitis,

to motivational intervention or a control group. MI corresponded to techniques outlined by Miller and colleagues (1988) and consisted of three separate discussions of the relationship of the patient's disease to continuous drinking and the offer of treatment. Both groups were given standard medical treatment and were encouraged to enter alcohol treatment. Outcome was evaluated for the period from the tenth to the sixteenth week after return to the community by patient interview and household contacts. There were no differences between the control and MI groups, approximately 38% of both groups remained abstinent for the 10-week interval. The authors conclude that the additional MI was not beneficial for these hospitalized alcoholic patients.

In an analysis of the alcohol treatment outcome literature, Miller and colleagues (1995) evaluated seven studies on motivational enhancement for alcohol problems that met their standards of methodological rigor and compared these studies with 30 other treatment modalities. These investigators used a Cumulative Evidence Score (CES) that represents a composite of several calculations and ratings, including methodological quality and outcomes at specific assessment and follow-up points. Five studies received favorable outcome ratings (Miller et al., 1988, 1993; Bien et al., 1993; Brown & Miller, 1993; Mallams et al., 1982), and two studies were reported as unfavorable for the motivational intervention (Kuchipudi et al., 1990; Chick et al., 1988). Overall the motivational enhancement obtained a CES score of +87 (min= +239; max= -239). Motivational enhancement was rated third among 30 other treatment modalities on the CES measure. In addition, these motivational interventions often cost the least to administer. Although these seven studies were termed motivational enhancement in the review, they included diverse interventions such as the Drinker Check-up, Motivational Interviewing, and extended advice. It was not clear how certain treatment components adhered to MI (e.g., Mallams et al., 1982; Chick et al., 1988). However, these motivational, brief interventions fared well in the comparison to the control group or other interventions studied with problem drinkers who are abusers or dependent on alcohol.

5.4. Motivational Enhancement in the Project MATCH Study

A more formalized, manual-driven alcoholism treatment developed for Project MATCH is called Motivational Enhancement Therapy (MET; Miller, Zweben, DiClemente, & Rychtarik, 1992). It is an individually administered, psychotherapeutic intervention based on the techniques of Motivational Interviewing and uses some of the types of feedback from the Drinker Check-up. MET consists of four treatment sessions preceded by an extensive assessment battery. Session 1 focuses on providing clients with clear, structured, personalized feedback compared to a reference group concerning their drinking status, typical level of intoxication, risk for developing a problem with alcohol, negative consequences of use, liver function and neurological tests, and drinking styles. The goal is to raise the clients' awareness of the extent to which alcohol has affected their lives and to build motivation for change. A copy of the feedback

report is given to the client to take home. Session 2 is designed to complete the feedback and to strengthen the commitment to change by using motivational interviewing techniques that are appropriate to where the clients are in their change process. Sessions 3 and 4 focus on reviewing progress, building a personal change plan, and renewing motivation. Termination is discussed at the end of the fourth session, and this involves reviewing motivational themes, summarizing the client's change process, eliciting self-motivational statements for the maintenance of change, and exploring future plans and areas of change.

The effectiveness of MET was evaluated and compared to two other treatments in Project MATCH, a national, multisite, clinical trial of alcoholism treatment matching with parallel outpatient and aftercare clients. The Project MATCH Research Group examined more than 20 a priori primary and secondary matching hypotheses generated to test the effects of matching clients to one of three different treatments based on various client characteristics (PMRG, 1997a,b, 1998a,b). The three treatments included (1) Cognitive Behavioral Therapy (CBT), grounded in social learning theory; (2) Twelve-Step Facilitation (TSF), based on the principles of Alcoholics Anonymous; and (3) MET, described earlier. Results indicated that all three treatments produced significant and long-lasting reductions in alcohol consumption and no one treatment substantially outperformed another. Outpatient alcoholics in MET did show slightly higher levels of drinking during treatment (PMRG, 1997b). However, post-treatment outcomes for all three treatments were not significantly different, with the exception that TSF had slightly higher levels of total abstinence.

Several interesting results emerged related to the interaction of MET with some patient characteristics and to the role of motivation in the treatment process.

1. A single weakly supported matching effect was found that involved MET and the less motivated outpatient clients (PMRG, 1997). When poorly motivated clients participated in MET, they had a higher percentage of days abstinent from alcohol compared to poorly motivated clients in CBT, as was hypothesized. However, this effect emerged only at the very end of the 12-month follow-up period but was not evident at the 3-year follow-up. Additional analyses found little evidence for a differential effect of MET with poorly motivated clients (DiClemente, Carbonari, Zweben, Morel, & Lee, 2001).
2. The strongest and most consistent matching effect of the trial also involved the MET treatment. Outpatient clients with higher baseline anger fared better in drinking outcomes after MET than with CBT or TSF, and those low in anger had better outcomes after TSF and CBT, compared to MET (PMRG, 1997b). It was assumed that those high in trait/state anger found that the message of personal responsibility and the lack of any struggle around resistance was particularly helpful. However, it has been difficult to pin down the exact reasons for the matching effect (Waldron, Miller, & Tonigan, 2001).

3. Other matching effects, although weaker, indicated that MET might be less beneficial for those patients who have greater alcohol dependence, psychiatric severity, and/or social networks supportive of drinking (Longabaugh & Wirtz, 2001; PMRG, 1997a,b, 1998b).
4. For outpatient participants, a pretreatment measure of client motivational readiness to change emerged as the single best predictor of drinking outcomes throughout the posttreatment period up to 3 years posttreatment (PMRG, 1998b). Readiness was measured using stage of change measure and creating a single score by adding together mean subscale scores for Contemplation, Action, and Maintenance and subtracting Precontemplation (DiClemente, Carbonari, Zweben, et al., 2001).
5. Pretreatment measures of motivation were not the only predictors of drinking outcomes related to motivational enhancement. Measures of abstinence self-efficacy, coping processes of change, and stage of change subscales taken at the end of treatment were also highly predictive of long-term drinking outcomes for both outpatient and aftercare clients (Carbonari & DiClemente, 2000; DiClemente, Carbonari, Zweben et al., 2001; DiClemente, Carbonari, Daniels, Donovan, Bellino, & Neavins, 2001).

Project MATCH findings supported an important role for motivational variables and motivational enhancement in treating alcohol abuse and dependence. MET emerged as a viable stand-alone individual therapy that could be used in traditional treatment settings. A MET therapy manual is available for clinicians and researchers to replicate these findings and to guide implementation of the techniques and tools of MI and MET (Miller et al., 1992). The number, duration, and distribution of MET sessions are flexible, so that briefer and more extensive versions could be tested. The goals of motivational enhancement therapy can be adapted to client goals, so that harm reduction may be used as an outcome. Although briefer in the number of sessions, a recent study that evaluated the cost-effectiveness of MET, compared with the CBT and TSF treatment modalities using the Project MATCH data, indicated that it cost twice as much or more per patient contact hour as CBT and TSF because of the extensive assessment (Cisler, Holder, Longabaugh, Stout, & Zweben, 1998). However, clinical replications of MET could be less costly to deliver.

5.5. Summary

Although initially motivational enhancement approaches were used to treat problem drinkers primarily in brief interventions, there is growing evidence that a more extensive version can be useful for outpatient and aftercare treatment settings as well as in nontraditional settings. Moreover, the same type of treatment can be used for reducing or eliminating other drugs of abuse in individuals with alcohol problems who are substance abusers and/or addicted to nicotine (Yahne & Miller, 1999). Motivational enhancement treatments can

also be used as adjunctive treatments or part of a stepped care approach to treatment. For example, Saunders, Wilkinson, and Phillips (1995) used a motivational intervention as an adjunctive treatment in a controlled clinical trial with illicit drug users who attended a methadone clinic. During the 6-month follow-up period, the motivational participants demonstrated more favorable outcomes across a variety of measures, compared to education controls. Barrowclough and colleagues (2001) added motivational interviewing to cognitive behavior therapy and family intervention for a dually diagnosed sample and found that it increased abstinence from alcohol and drugs, compared with routine care. A recent Treatment Improvement Protocol distributed by the Center for Substance Abuse Treatment described how motivational approaches could be integrated into current treatment programs (CSAT, 1999). However, it is difficult to identify the active ingredients and evaluate their impact when eclectic or multiple treatments are administered simultaneously.

Motivational enhancing interventions ranging from briefer versions that include single sessions or extensive feedback (DCU) to more extensive ones (MET) demonstrated a broad range of utility in treating alcohol abuse and dependence. Motivational interventions can be used as independent, stand-alone interventions, adjunctive treatments, and aftercare treatments to motivate continued abstinence, or can be integrated with other treatment approaches. In addition, this type of approach is particularly useful for individuals with higher levels of trait anger. There is an important role for these types of interventions, but there may also be some limitations in producing total abstinence in clients who have greater severity and alcohol-filled social networks. Additional research is needed to evaluate the scope or range of effectiveness, utility in various settings (court referral, outpatient alcohol treatment, medical, EAP), and the best way it can be combined with other treatments (pharmacological, behavioral, mutual-help groups).

6. Current Status and Future Directions

By examining past research findings and more current studies, we can draw some conclusions about the use of psychotherapy and motivational interventions in treating alcohol abuse and dependence. There is little support for dynamically oriented treatment, except for interpersonal/interactional groups that may have some matching potential. Cognitive Therapy is an appealing approach because of the cognitive disturbances that are encountered in alcoholism treatment. Few controlled studies that focus solely on Cognitive Therapy have been conducted, and they are inconclusive regarding the effectiveness of the specific cognitive aspects of the treatment. Motivational approaches have received substantial support in treating alcohol abuse and moderate support in treating dependence. The nature and extent of the effectiveness of this treatment or family of treatments require replication, additional research examining subcomponents and mechanisms of action, and effectiveness studies.

Specific recommendations for future research based on this review of the literature are as follows.

1. Although support is growing for using motivational interventions with alcohol problems, there is a need for effectiveness studies on these interventions, particularly MET, since it is being adopted widely as a result of the availability of the MATCH manuals and an increasing interest in motivation. The scope of efficacy and limits of effectiveness should be determined to provide guidance to clinical practice.
2. Additional controlled studies of Motivational Enhancement Therapies are needed to evaluate the critical active ingredients of these types of interventions. In particular, the personalized feedback that is a particularly costly part of this briefer intervention, as well as the interpersonal delivery style, optimal length of treatment, and appropriate type of setting, should be examined. Replications of efficacy studies in clinical settings with problem drinkers and dependent drinkers are also needed, as are additional cost–benefit studies.
3. Cognitive therapies and more purely cognitive interventions should receive more attention in research studies. Evaluations of these types of treatments for alcohol abuse and dependence are few in number. Critical aspects of these interventions should be evaluated to understand the role of changing cognitions and problematic thinking and belief systems in recovery from alcohol problems.
4. There is a need for research in the way to combine both cognitive therapy components and motivational interventions with other types of treatments, be they pharmacological, behavioral including contingency management, mutual-help groups, or relapse prevention. Since attribute treatment interactions (ATI) and the matching hypothesis have received only minimal support, combinations of treatments that have proposed different mechanisms of action and different targets of intervention should be considered. If we can identify diverse mechanisms of action that complement each other in producing change in drinking behavior and associated problems (motivation, beliefs, expectancies, work ethic, social skills, psychopathology), we can begin to use synergistically a variety of psychotherapy, behavioral, and pharmacological treatments to remediate these problems. A functional, mechanism-specific approach to tailoring treatments may be more effective than a more global matching one.
5. There is a pressing need to evaluate the way cognitive, interpersonal, and motivational types of treatments influence critical change moderators and mediators. One lesson from Project MATCH was that clients in very different treatments, including MET and CBT, produced equivalent outcomes on intervening variables, such as temptation to drink, abstinence self-efficacy, and processes of change, as well as on drinking outcomes. These variables measured at posttreatment, in turn, were

predictive of 1- and 3-year drinking outcomes (Carbonari & DiClemente, 2000). A better understanding of how to influence cognitive, motivational, behavioral, and social variables related to drinking outcomes would advance our ability to combine treatments more efficiently (Longabaugh & Wirtz, 2001).

Research studies and support for psychotherapy and motivational enhancement treatments that specifically target alcohol problems have grown during the past 15 years. In particular, treatment professionals have shown increasing interest in motivational approaches to treatment due in some measure to the increase of mandated treatment and early intervention. There continue to be a number of interesting areas for research that could enhance our understanding of these treatments for alcohol abuse and dependence. Both small and large scientific initiatives are needed. Small-scale research projects can be used in evaluating components and offering direction for constructing large-scale research that would consist of efficacy and effectiveness studies that could determine the types of people and settings that could benefit from these types of interventions.

References

- Barrowclough, C., Haddock, G., Tarrier, N., Lewis, S.W., Moring, J., O'Brien, R., Schofield, N., & McGovern, J. (2001). Randomized controlled trial of motivational interviewing, cognitive/behavior therapy, and family intervention for patients with comorbid schizophrenia and substance use disorders. *American Journal of Psychiatry* 158(10), 1706–1713.
- Beck, A.T. (1976). *Cognitive Therapy and the Emotional Disorders*. New York: International Universities Press.
- Beck, A.T., Wright, F.D., Newman, C.F., & Liese, B.S. (1993). *Cognitive Therapy of Substance Abuse*. New York: Guilford.
- Bien, T., Miller, W., & Boroughs, J. (1993). Motivational interviewing with alcohol outpatients. *Behavioral and Cognitive Psychotherapy* 21, 347–356.
- Bombardier, C.H., & Rimmele, C.T. (1999). Motivational interviewing to prevent alcohol abuse after traumatic brain injury: A case series. *Rehabilitation Psychology* 44, 52–67.
- Brown, J.M., & Miller, W.M. (1993). Impact of motivational interviewing on participation and outcome in residential alcoholism treatment. *Psychology of Addictive Behaviors* 7, 211–218.
- Carroll, K.M. (1999). Behavioral and cognitive behavioral treatments. In B.S. McCrady and E.E. Epstein (eds.), *Addictions: A Comprehensive Guidebook*. New York: Oxford University Press, pp. 250–267.
- Carroll, K.M., & Schottenfeld, R. (1997). Nonpharmacologic approaches to substance abuse treatment. *Medical Clinics of North America* 81, 927–944.
- Chick, J., Ritson, B., Connaughton, J., Stewart, A., & Chick, J. (1988). Advice versus extended treatment for alcoholism: A controlled study. *British Journal of Addiction* 83, 159–170.
- Cisler, R., Holder, H.D., Longabaugh, R., Stout, R.L., & Zweben, A. (1998). Actual and estimated costs for alcohol treatment modalities: Case study from Project MATCH. *Journal of Studies on Alcohol* 59, 503–512.
- Cooney, N.L., Kadden, R.M., Litt, M.D., & Getter, H. (1991). Matching alcoholics to coping skills or interactional therapies: Two-year follow-up results. *Journal of Consulting and Clinical Psychology* 59, 598–601.
- Crumbach, J.C., & Carr, G.L. (1979). Treatment of alcoholics with logotherapy. *International Journal of the Addictions* 14, 847–853.
- CSAT Treatment Improvement Protocol Number 35. (1999). Enhancing Motivation for Change in Substance Abuse Treatment. DHHS.

- DiClemente, C.C. (1999). Motivation for change: Implications for substance abuse. *Psychological Science* 10(3), 209–213.
- DiClemente, C.C., Bellino, L.E., & Neavins, T.M. (1999). Motivation for change and alcoholism treatment. *Alcohol Health and Research World* 23 (2), 86–92.
- DiClemente, C.C., Carbonari, J., Zweben, A., Morrel, T., & Lee, R.E. (2001). Motivation hypothesis causal chain analysis. In R. Longabaugh and P.W. Wirtz (eds.), *Project MATCH Hypotheses: Results and Causal Chain Analyses*. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series, Volume 8. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, pp. 206–222.
- DiClemente, C.C., Carbonari, J.C., Daniels, J.W., Donovan, D.M., Bellino, L.E., & Neavins, T.M. (2001). Self-efficacy as a matching hypothesis: Causal chain analysis. In R. Longabaugh and P.W. Wirtz (eds.), *Project MATCH Hypotheses: Results and Causal Chain Analyses*. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series, Volume 8. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, pp. 239–259.
- DiClemente, C.C., Carbonari, J.P., & Velasquez, M.M. (1992). Alcoholism treatment mismatching from a process of change perspective. In R.R. Watson (ed.), *Treatment of Drug and Alcohol Abuse*. Totowa, NJ: Humana Press, pp. 115–142.
- DiClemente, C.C., & Hughes, S.O. (1990). Stages of change profiles in alcoholism treatment. *Journal of Substance Abuse* 2, 217–235.
- DiClemente, C.C., & Prochaska, J.O. (1998). Toward a comprehensive, transtheoretical model of change: Stages of change and addictive behaviors. In W.R. Miller and N. Heather (eds.), *Treating Addictive Behaviors*, 2nd ed. New York: Plenum, pp. 3–24.
- Ellis, A., McInerney, J.F., & DiGiuseppe, R. (1988). *Rational-Emotive Therapy with Alcoholics and Substance Abusers*. Elmsford, NY: Pergamon.
- Gentilello, L.M., Rivara, F.P., Donovan, D.M., Jurkovich, G.J., Daranciang, E., Dunn, C.W., Villaveces, A., Copass, M., & Ries, R.R. (1999). Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. *Annals of Surgery* 230, 473–483.
- Handmaker, N.S., Miller, W.R., & Manicke, M. (1999). Findings of a pilot study of motivational interviewing with pregnant drinkers. *Journal of Studies on Alcohol* 60, 285–287.
- Heather, N., Rollnick, S., Bell, A., & Richmond, R. (1996). Effects of brief counselling among male heavy drinkers identified on hospital wards. *Drug & Alcohol Review* 15, 29–38.
- Isenhart, C. (1994). Motivational subtypes in an inpatient sample of substance abuser. *Addictive Behaviors* 19, 463–475.
- Kadden, R.L., Cooney, N.L., Getter, H., & Litt, M.L. (1989). Matching alcoholics to coping skills or interactional therapies: Posttreatment results. *Journal of Consulting and Clinical Psychology* 57, 698–704.
- Kelly, A.B., Halford, W.K., & Young, R.M. (2000). Maritally distressed women with alcohol problems: The impact of a short-term alcohol-focused intervention on drinking behaviour and marital satisfaction. *Addiction* 95, 1537–1549.
- Kassin, B., Platz, A., & Su, W.H. (1970). Social and psychological factors in the treatment of chronic alcoholism. *Journal of Psychiatric Research* 8, 13–27.
- Kuchipudi, V., Hobein, K., Flickenger, A., & Iber, F.L. (1990). Failure of a 2-hour motivational intervention to alter recurrent drinking behavior in alcoholics with gastrointestinal disease. *Journal of Studies on Alcohol* 51, 356–360.
- Levinson, T., & Sereny, G. (1969). An experimental evaluation of insight therapy for the chronic alcoholic. *Canadian Psychiatric Association Journal* 14, 143–146.
- Levy, M. (1997). Group therapy in addictive and psychiatric disorders. In N.S. Miller (ed.), *The Principles and Practice of Addictions in Psychiatry*. Philadelphia, PA: Saunders, pp. 385–391.
- Litt, M.D., Babor, T.F., DelBoca, F.K., Kadden, R.M., & Cooney, N.L. (1992). Types of alcoholics, II: Application of empirically derived typology to treatment matching. *Archives of General Psychiatry* 49, 609–614.
- Longabaugh, R., & Wirtz, P.W. (eds.) (2001). *Project MATCH Hypotheses: Results and Causal Chain Analyses*. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series, Volume 8. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism.

- Longabaugh, R., Woolard, R.F., Nirenberg, T.D., Minugh, A.P., Becker, B., Clifford, P.R., Carty, K., Sparadeo, F., & Gogieni, A. (2001). Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department. *Journal of Studies on Alcohol* 62(6): 806–816.
- Mallams, J.H., Godley, M.D., Hall, G.M., & Meyers, R.J. (1982). A social-systems approach to resocializing alcoholics in the community. *Journal of Studies on Alcohol* 43, 1115–1123.
- Matano, R.A., & Yalom, I.D. (1991). Approaches to chemical dependency: Chemical dependency and interactive group therapy: A synthesis. *International Journal of Group Psychotherapy* 41, 269–293.
- Miller, W.R. et al. (1995). What works? A methodological analysis of the alcohol treatment outcome literature. In R.K. Hester and W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*. Boston: Allyn & Bacon, pp. 12–44.
- Miller, W. R., & Rollnick, S. (1991). *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford.
- Miller, W.R., Benefield, R.G., & Tonigan, J.S. (1993). Enhancing motivation for change in problem drinking: A controlled comparison of two therapist styles. *Journal of Consulting and Clinical Psychology* 61, 455–161.
- Miller, W.R., Sovereign, R., & Krege, B. (1988). Motivational interviewing with problem drinkers: II. The Drinker's Check-up as a preventive intervention. *Behavioural Psychotherapy* 16, 251–268.
- Miller, W., Zweben, A., DiClemente, C.C., & Rychtarik, R.G. (1992). *Motivational Enhancement Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals With Alcohol Abuse and Dependence*. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series, Volume 2. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism.
- Monti, P.M., Spirito, A., Myers, M., Colby, S.M., Barnett, N.P., Rohsenow, D.J., Woolard, R., & Lewander, W. (1999). Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *Journal of Consulting and Clinical Psychology* 67(6), 989–994.
- Ojehagen, A., Berglund, M., Appel, C.P., Andersson, K., Nilsson, B., Skjaerris, A., & Wedlin-Toftenow, A.M. (1992). A randomized study of long-term out-patient treatment in alcoholics. *Alcohol & Alcoholism* 27(6), 649–658.
- Project MATCH Research Group. (1997a). Matching alcoholism treatments to client heterogeneity: Project MATCH post-treatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–29.
- Project MATCH Research Group. (1997b). Project MATCH secondary a priori hypotheses. *Addiction* 92(12), 1671–1698.
- Project MATCH Research Group. (1998a). Matching alcoholism treatments to client heterogeneity: Treatment main effects and matching effects on drinking during treatment. *Journal of Studies on Alcohol* 59, 631–639.
- Project MATCH Research Group. (1998b). Matching alcoholism treatments to client heterogeneity: Project MATCH three year drinking outcomes. *Alcoholism Clinical and Experimental Research* 22, 1300–1311.
- Quigley, L.A., & Marlatt, G.A. (1999). Relapse prevention: Maintenance of change after initial treatment. In B.S. McCrady and E.E. Epstein (eds.), *Addictions: A Comprehensive Guidebook*. New York: Oxford University Press, pp. 370–395.
- Roth, A., & Fonagy, P. (1996). Alcohol dependency and abuse. In A. Roth and P. Fonagy (eds.), *What Works for Whom? A Critical Review of Psychotherapy Research*. New York: Guilford, pp. 216–233.
- Rounsaville, B.J., & Carroll, K.M. (1993). Interpersonal psychotherapy for drug users. In G.L. Klerman & M.M. Weissman (eds.), *New Applications of Interpersonal Psychotherapy*. Washington, DC: American Psychiatric Association Press.
- Saunders, B., Wilkinson, C., & Phillips, M. (1995). The impact of a brief motivational intervention with opiate users attending a methadone programme. *Addiction* 90, 415–44.
- Yalom, I.D. (1995). *The Theory and Practice of Group Psychotherapy*, 4th ed. New York: Basic Books.
- Zimberg, S. (1974). Evaluation of alcoholism treatment in Harlem. *Quarterly Journal of Studies on Alcohol* 35, 550–557.

- Waldron, H.B., Miller, W.R., & Tonigan, J.S. (2001). Client anger as a predictor of differential response to treatment. In R. Longabaugh & P.W. Wirtz (eds.), *Project MATCH Hypotheses: Results and Causal Chain Analyses*. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series, Volume 8. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism, pp. 134–148.
- Yahne, C.E., & Miller, W.R. (1999). Enhancing motivation for treatment and change. In B.S. McCrady & E.E. Epstein (eds.), *Addictions: A Comprehensive Guidebook*. New York: Oxford University Press, pp. 235–249.

Involvement of Support Networks in Treatment

Richard Longabaugh

Abstract. Alcohol dependence and abuse are biopsychosocially determined and ameliorated. However, social factors involved in effecting treatment outcomes continue to be understudied as a context in which psychological and biological factors are researched and also as a treatment focus in their own right. Yet the client's social setting and relationships during and after treatment are more important forces in the recovery process than formally defined alcohol treatment interventions. Though this has been so historically, it is even more likely now in managed care environments where treatments are highly circumscribed. This suggests that treatment interventions refocus toward targeting changes in the patient's social environment.

Treatments involving spouses and families of the patient's social networks it has been shown, are incrementally effective. A high priority for research is to identify the set of conditions under which the wider social network can also be effective. Early results are promising though not well understood. The next generation of network therapies will focus on testing the conditions under which various components of the patient's social network are important in affecting patient outcomes. As with other therapies, an important focus for research is on identifying the active ingredients in these treatments that bring about favorable change in patients generally or that enhance the outcomes of the subset of patients particularly amenable to network interventions (patient-treatment "matching").

Recommended priorities for future research in network interventions are identified.

Alcohol dependence and abuse are biopsychosocially determined and ameliorated. The three components of this widely accepted premise are not equally attended to in the research priorities of either NIAAA or the scientists who seek to build the knowledge base. Historically, a great deal of effort has been spent in attempting to identify the psychological factors implicated in the development of alcohol dysfunctions and in developing psychological and behavioral treatments that aim to reduce them. More recently, as the technology

has developed, research has begun to focus on the biological sources and mechanisms involved in the development of alcohol dysfunctions. With the development of pharmacology, new pharmacological agents have become a prominent focus for interventions that will reduce and/or prolong return to alcohol misuse. In contrast, social factors involved in the development and treatment of alcoholism continue to be an understudied context in which biological and psychological factors are researched. Yet, as identified by Seldan Bacon more than 25 years ago (1973), the client's social setting and relationships during and after treatment are more important forces in the recovery process than alcohol treatment professionals. This observation has been supported by studies of the factors that are predictive of remittance and relapse in long-term outcomes of patients treated for alcohol dependence, as well as untreated problem drinkers (e.g., Humphreys, Moos, & Cohen, 1997). These studies were conducted when patient populations received ample amounts of treatment. In the current environment of managed care which has limited the amount of treatment that patients may receive, the impact of treatment is even less likely to be sustained during any period of time. In fact, studies of treatment outcomes have repeatedly demonstrated that treatment effects, however impressive during the course of treatment, quickly diminish after treatment is completed. Not only do two-thirds of relapses occur during the first 3 months after treatment is completed (Connors, Maisto, & Donovan, 1996), but treatment factors are minor contributors in accounting for the variance evident in relapse (Humphreys, 1997). As yet, neither pharmacotherapies nor individually focused psychological and behavioral treatments developed can consistently demonstrate sustained effects beyond treatment completion.

Putting these two observations together—that treatment has short-lived effects and that social environmental factors are the most robust predictors of long term outcome—leads to the obvious hypothesis that treatments should target changing the patient's social environment as a primary focus for intervention. Within the field of alcohol treatment, there has been an underdeveloped line of research that has pursued this hypothesis. The present review focuses on one part of this research—the involvement of social network members in treatment. Omitted from this review is the likely important role played by the broader context of the social environment that is also an important part in influencing the lives of those impaired by alcohol abuse or dependence.

To set boundaries on this review, the social network is defined as one or more people residing outside of the community of treatment providers with whom the patient may have direct interpersonal contact and interaction. (This omits a potentially very important source of influence—people to whom the patient may be exposed, but not have interaction, e.g., people viewed in mass media who may have considerable influence on the patient, but with whom the patient has no direct reciprocal influence.)

1. Self-Help Groups

The social network may be conceptually divided into two subtypes, the preexisting everyday social network in which the patient may be embedded prior, during, and following treatment, and networks developed specifically to facilitate the patient's recovery, that is, mutual self-help groups. Alcoholics Anonymous, the most prevalent and prominent of mutual self-help groups, is reviewed elsewhere in this volume by Humphreys (Self-Help and Twelve-Step Groups). Consequently this review will not focus on Alcoholics Anonymous (AA).

Research on mutual self-help groups other than AA is largely nonexistent in the United States. This omission needs to be addressed. No doubt one factor in this omission is the lack of availability of such groups for researchers, and also for patients in search of them. However, during the past decade, several such groups have come into existence, and they vary considerably in their ideology, target population, and orientation toward abstinence. First, research needs to test their effectiveness, as adjuncts to concurrent treatment and/or as a posttreatment factor. Second, these groups have arisen primarily as a reaction to one or more perceived limitations of Alcoholics Anonymous. Thus, one self-help group emphasizes moderation as opposed to life long abstinence as a goal (Moderation Management). Rational Recovery and SMART Recovery deemphasize concepts such as powerlessness and loss of control and emphasize the importance of reason and logic in self-directed change; SMART emphasizes cognitive behavioral mechanisms for change. The Secular Organization for Sobriety shares a disease orientation with AA but does not emphasize spirituality and a higher power; Women for Sobriety narrows the focus to a gender-specific philosophy of personal empowerment.

A fundamental research priority is to determine the effectiveness of these alternative self-help networks. Once effectiveness has been established, then it is important to investigate the theoretical question as to the shared and unique ingredients among groups that bring about change. An obvious research question is whether these groups are better matched to patients with personal characteristics that are putatively better suited to the stated goals and recovery strategies of the groups. If it were found that matching to type of self-help group were important to recovery, this could provide a great impetus for increasing the availability of such groups.

Still another matching question of great interest concerns the compatibility of the philosophy and other characteristics of the self-help group with that of the treatment that the patient receives. This is an intuitively appealing hypothesis, but little research has been conducted to test it. McCrady, Epstein, and Hirsh (1999) reported that the combination of AA and Alcohol Behavioral Couples Therapy (ABCT) is less useful for patients on some measures of outcome (time to first heavy drinking day and/or shorter drinking episodes) than those treated either by ABCT alone or a combination of ABCT and Relapse Prevention.

Project MATCH results suggest that AA involvement may help patients treated in various therapies but is more helpful to patients with natural networks supportive of drinking when treated in a compatible Twelve-Step therapy than when treated in Cognitive Behavioral Therapy (Longabaugh, Wirtz, Zweben, & Stout, 1998).

Certainly the question of the effect of length of involvement with a self-help group needs to be carefully studied. In MATCH, involvement in AA diminished markedly during the study period, yet matching effects having to do with AA involvement paradoxically increased over time (Longabaugh et al., 1998). Is this true of other self-help groups, or is this effect unique to AA?

An important question for all of these constructed social networks is whether and how involvement in these networks interacts with the preexisting social networks in which the patient may be embedded. The previously cited research of Longabaugh et al. (1998) suggests that involvement in a self-help group such as AA can counteract the long-term poor prognostic effect of support for drinking from the patient's natural network. However, little is known about the circumstances under which involvement in one or another self-help group facilitates or impedes the patient's relationships to members of preexisting social networks. Patients with greater investment in supportive preexisting social networks may not find self-help groups as valuable, and may find that this involvement increases role strain between themselves and significant others involved as role reciprocals in these relationships. Complex research designs would no doubt be required to tease out such complex interactions as these. A host of such questions beg to be addressed. However, they must await the completion of more basic research testing the overall effectiveness of these various self-help groups.

2. Treatment Involvement by Members of the Natural Social Network

The unique focus of this chapter is consideration of involvement by members of the patient's natural social network in treatment. This network may include a wide variety of role reciprocals—spouses, parents, children, extended family, people with whom one does business, co-workers, recreational partners, fellow-worshippers, friends, etc. Yet when the literature is perused for research involving others in the patient's social network in treatment, only two categories in the patient's network have received any sustained attention—spouse and family involvement. Thus, most of what is currently known about involvement of the patient's social network in treatment is limited to these two categories—and of these, spouse involvement is much more prominent.

Before looking at these areas specifically, it will be useful to describe a taxonomy for classifying involvement of network members in treatment. Several differentiations are important, setting the stage for basic research questions in this area. Table 1 maps the outline for the taxonomy and places better known examples of each of these treatments within it.

Table 1. Basic Taxonomy and Classifications

Named Intervention	Who is Involved in Treatment?						What is the Focus of Treatment?	
	Kin			Nonkin			Alcohol Specific	Relationship Enhancement
	Spouse	Selected Family Members	Entire Family	Patient	Friends	Work Associates		
ABCT	X			X			X	X
Family Therapy			X	X				X
Johnson Intervention			X	XX ^a			X	
ARISE		X		XX ^a	X	X	X	
CRAFT	X	X					X	
CRA Network Therapy	X	X		X	X	X	X	Xp ^b
COMBINE		X		X	X	X	X	
CBI Unilateral Therapy	X						X	
Broad Spectrum Therapy	X	X	X	X	X	X	X	X

A first distinction is, who is intended to be involved in the treatment? The major division is kin and/or nonkin. Among kin, the next subdivide is spouse (e.g., as in behavioral marital therapy) versus one or more selected members or all of the immediate family (e.g., family therapy). When moving outside of kinship relationships, friends and role reciprocals from work are the primary distinctions made (sometimes described as "buddy systems" or more generally "support systems").

Crosscutting all of these distinctions is the question whether the patient is to be (immediately or subsequently) involved in the intervention. In unilateral therapy (Thomas, Santa, Bronson, & Oyserman, 1987), patients are not present because they choose not to be. In a Johnson Intervention, or one of its derivations, such as ARISE, the patient is omitted from planning the intervention by the intention of the therapist.

Another major distinction among network therapy interventions is the focus of the intervention: in some cases it may simply be education about alcoholism. More typically, the focus is changing the behaviors of patient and/or role reciprocals with regard to alcohol use. More extensive intervention involves directly trying to enhance the relationship between patient and role reciprocal. A still broader focus is when the entire social unit is the focus of

change, such as in most family therapies, sometimes including the relationship of the unit members to the wider network in which they exist.

Within each of these categorizations, the usual questions of frequency, intensity, and duration of network involvement need to be addressed. And finally, there is the question of the putative methods of action by which the change is to take place: that is, how is it that the intervention accomplishes its intended changes?

If all or even some of these distinctions are important to the effectiveness of the intervention, it becomes readily apparent that research-based knowledge regarding involving the network in therapy is exceedingly sparse.

When the critical questions of for whom the therapy is beneficial and contraindicated are added, it becomes crystal clear that this potentially important resource for enhancing treatment effects is virtually an unknown domain.

2.1. Marital and Family Therapy for Alcohol Abusers

Analyses across studies of the effectiveness of spouse and family involvement in treatment for alcohol (McCrady, 1989; O'Farrell, 1986, 1989; O'Farrell & Fals-Stewart, 2000) and other substance abusers (Fals-Stewart, O'Farrell, Feehan, Birchler, Tiller, & McFarlin, 2000; Stanton & Shadish, 1997) have demonstrated that including them enhances treatment effectiveness. When meta-analyses have been used to measure the effect with addiction to other substances (Stanton & Shadish, 1997), the effect size is sufficient to lead to the question, why doesn't all treatment for alcohol troubled patients include the spouse and/or family? One obvious answer is that a large percentage of alcohol troubled patients do not have spouses, though a much smaller number are without proximally located families of any kind. So, by definition, only a percentage of alcohol patients can qualify for family therapy, and a considerably smaller percentage for marital therapy. Therefore the applicability of approaches involving spouses and families treatment to those involving other elements of the patient's social network will be limited unless ways can be found to extend these models to apply to these other relationships within the patient's network.

2.1.1. Marital Therapy. The bulk of marital therapy has been done within the context of a cognitive behavioral conceptual model (McCrady & Epstein, 1995; O'Farrell, 1986). Most studies have shown that the addition of behavioral marital therapy for alcohol abusers enhances the functioning of the couple and is also likely to enhance the identified client's drinking outcomes (Epstein & McCrady, 1998; Fals-Stewart et al., 2000). This effect is most apparent in the short term. This has led researchers to add components to the basic marital therapy program, such as more sessions with a relapse prevention component following treatment. O'Farrell and colleagues found that adding such a component did maintain better outcomes, especially for those whose prognosis was initially poorer (O'Farrell, Choquette, & Cutter, 1998).

In the early years, behavioral marital therapy for alcoholics treatment research was offered to patients who met fairly restrictive inclusion and exclusion criteria—often a fairly select group. However, in recent years, the Alcohol Behavior Couples Therapy model (ABCT) is being applied to more heterogeneous groups of patients (Epstein & McCrady, 1998). The obvious research question is to determine whether this approach can be adapted successfully to a wider range of patients with other problems besides alcohol. Certainly, poly-drug abuse patients are a more common phenomenon now than in the past. The reported success of Fals-Stewart and colleagues in applying ABCT to this population (Fals-Stewart, Birchler, & O'Farrell, 1996) suggests broadened applicability for this approach. Similarly, the research of O'Farrell demonstrating matching effects of longer treatment to those with more severe marital problems (O'Farrell et al., 1998) suggests the generic hypothesis that dose can be matched to assessed need.

One marital problem that is frequently associated with alcohol or drug abuse is marital violence. Violent patients were previously excluded from research protocols because of the risks involved. Recently however, O'Farrell & Murphy (1995; O'Farrell, Van Houton, & Murphy, 1999) have shown that ABCT can be successfully applied to this population as well, with an accompanying reduction in acts of violence in the relationship. This research needs to be extended to alcoholic populations as well.

As in any therapy, not all patients benefit equally from behavioral marital therapy. More effort must be undertaken to identify those who will fare better in some form of therapy other than couples therapy. Patient-treatment matching has not been a fruitful way of enhancing patient drinking outcomes when contrasting individual therapies (Project MATCH Research Group, 1997a,b, 1998). However, research matching patients to individual cognitive behavioral therapy (CBT) versus CBT plus a relational enhancement component has been more successful (Longabaugh, Wirtz, Beattie, Noel & Stout, 1995). The results of this study were that small doses of relational enhancement were most helpful for patients who had nonproblematic relationships with their significant others. Extended relational enhancement therapy was more effective during the 18 month follow-up period for those who were either less invested in a relationship supportive of the patient's abstinence or were more invested in a relationship that was supportive of the patient's drinking. Extended relationship therapy was ineffective for patients who had low investment in relationships that were also unsupportive of abstinence. A 4-year follow-up of these groups however, indicated that the drinking outcomes of patients treated in the eight sessions of extended relationship therapy who, prior to treatment were more invested in a relationship supportive of drinking, markedly deteriorated during the longer period (Stout, Longabaugh, Gogineni, Rice, Beattie & Noel, 1996). This raises the question how long relationship therapy should go on. A reasonable hypothesis that is important to test is whether the effectiveness of marital therapies for alcohol abusers can be sustained by lengthening the duration of treatment for much longer periods of time, perhaps almost indefinitely.

by including of annual marital check up sessions. Surely the cost-benefit of such an intervention might be quite favorable (e.g., Fals-Stewart, O'Farrell, & Birchler, 1997). In this context, it should be noted that there is a remarkable inconsistency in the alcohol treatment research community where the effectiveness of a pharmacotherapy is evaluated by the reduction in the patient's drinking while the patient is taking the medication. In contrast, in psychosocial therapies, treatment effectiveness is ordinarily evaluated at a point considerably after the treatment has been completed, often times 6 months or a year later. When treatment effects dissipate during the posttreatment period, we are likely to judge the treatment as ineffective. As noted, this criterion is not applied in the same manner to pharmacotherapies.

Even though behavioral marital therapy has been proven effective, it is not yet clear why it is effective. As with every other form of treatment for alcohol abusers, we must focus research efforts on identifying the active ingredients of treatment (Morgenstern & Longabaugh, 2000; Longabaugh & Wirtz, 2001). Only by doing so will we be able to incorporate these ingredients into refined treatment protocols that will combine the most robust components of the intervention.

By successfully identifying active ingredients, it is possible to test broadening the intervention to include members of the patient's network who are not spouses, to see whether the same combination of ingredients can be applied to a more heterogeneous patient population and enhance overall treatment effectiveness.

Still another question regarding applying couples therapy more widely is why the treatment community does not heavily use this modality. Technology transfer studies need to be conducted to make this therapy widely available to suitable patients.

2.1.2. Unilateral Spouse Therapy. The early work of Thomas on intervening with the spouses of alcohol abusers who are unwilling to seek treatment themselves, it has been shown is highly beneficial (Thomas et al., 1987; Thomas & Ager, 1993). More recent work, stemming from the early research of Azrin, Sisson, Meyers and Godley (1982) carried out by Miller, Meyers, and Tonigan (1999) with a model labeled CRAFT (Community Reinforcement and Family Training) has replicated the finding that these spouses have improved psychosocial outcomes and CRAFT is also much more likely to result in the alcohol abusing spouse getting into treatment in the first 6 months following the intervention than either a Johnson Intervention or especially Alanon.

An obvious question is, who else in the patient's network may be able to accomplish the same effect. A parent or a sibling may be a more influential mediator than a spouse. And what about other people in the network who are important to the patient: can they have the same effect?

Still another variation of unilateral intervention has evolved from the initial Johnson Intervention: The ARISE Intervention (Garret, Landau, Shea, Stanton, Baciewicz, & Brinkman-Sull, 1998). This method is less confrontational, takes

into account the needs of the chemically dependent person as well the needs of the larger family and network system, and aims at enrolling substance abusers in outpatient as well as inpatient treatment. Moreover, the intervention is tailored to the readiness of the family and network to intervene. The ARISE Intervention appears to have considerable promise, at least on the basis of preliminary work.

The cumulative evidence suggests that interventions involving various elements of the network to change the targeted behavior of the addicted person and bring them into treatment are effective. What is less clear is what kinds of patients, networks, and contexts will respond best to these various kinds of unilateral interventions. As all are likely to show some effectiveness, main effect comparisons are not likely in themselves to yield great information. Rather, it is likely that some of these models will be more suitable for certain kinds of patients, networks, and circumstances than others. Investigations taking into account acuteness of crisis versus chronicity, degree of conflict, and cohesiveness in the identified unit; alienation of patient from the network; and other likely important variables need to be conceptualized and tested. It is likely that only with further development of theory will it be possible to identify which type of intervention is best for whom.

When the focus moves from couples to family therapy, findings become more equivocal. We were unable to identify any studies of family behavioral therapy. Perhaps a family is too complex a unit to which to apply a simple behavioral model. Instead, interventions guided by systems theory have been conducted. There are too few of them to draw any conclusions. Therefore the question still to be answered for such interventions is that of their effectiveness over and above what can be achieved by intervention with a single relationship extracted from the family.

2.2. Moving Outside of the Family Unit

A much less researched question, though one that is now prominent, is whether other members of the network outside of the family can be brought into treatment to enhance outcomes. Can one or more others be incorporated into the treatment? An exploratory study by Longabaugh, Clifford, and Wirtz (1995) suggests that including someone other than the spouse with the patient in treatment will also have a beneficial effect, though not as beneficial. If so, what are the criteria that should be used for selecting such an ally? Two models are readily apparent and need to be tested for their comparative effects.

2.2.1. Treatment Supporters. Galanter and colleagues developed and are conducting tests of involvement of the members of the larger network as supporters of the treatment effort (Galanter, 1993). Full-scale research on this model, labeled Network Therapy, is still in process, and preliminary results are highly encouraging. In this model, involvement of network members is solely to support the client in treatment. Early involvement by network members

helps clients to stay in treatment during the initial phase when they are most likely to drop out (Galanter, 1993; Stanton & Shadish, 1997) and also helps to provide a long-term social context that is supportive of sobriety (Humphreys et al., 1997). In this model, there is no aim to enhance the relationship of network members to patient, other than that which would result from their support and the improved drinking status of the patient, if achieved.

A test to contrast two variations in thrust for incorporating network members into the treatment is very intriguing. In one variation, network members are selected for inclusion in treatment because they have been identified as healthy forces for supporting treatment goals and patient sobriety. This is the approach being adapted for including supportive significant others in Project COMBINE behavioral treatment (Miller, 1999). Another variation, however, is to incorporate into the treatment members of the network who themselves are alcohol abusers. As in smoking research, the idea is to couple together in alliance those who are trying to deal with their own problem. This is the modus operandi of mutual self-help groups. It could be carried a step further by asking members of the patient's natural social network, who are not initially supporters of the therapy or themselves ready to change, to participate in the treatment to help the identified patient. This approach has been conducted with perinatal women with a cocaine problem with some preliminary success (Egelko, Galanter, Dermatis, & DeMaio, 1998). The research question is, under what set of conditions is it helpful to bring in this less supportive component of a patient's social network to ally with the treatment intervention? Certainly, for some network members, a commitment to helping a friend would be easier to execute than a commitment to help themselves. A more generic question is, what are the boundaries for using the network in this manner?

2.2.2. Enhancing Network Relationships. A more ambitious model for network involvement would be aimed at actually changing the nature of the patient's relationships with network members to enhance the value of the relationship to patient and network member alike. This is the model underlying ABCT, where the goal is to change the contingencies of the spouse's behavior toward the patient around alcohol and also to increase the value of the relationship for both participants, thus increasing their interdependency. Expanding this model to the larger network of the patient is more problematic in implementation. But it also might be more long lasting in its effectiveness when successful, because each participant in a relationship with the patient would have a greater stake in the effect of the treatment. The Community Reinforcement Approach (CRA) (Meyers & Miller, 2001; Smith, Meyers, & Miller, 2001), elsewhere reviewed for this volume by Kadden, implicitly embraces this approach. Not only is the patient to be reinforced by members of the larger community for sobriety, but also these other members need to be reinforced by the patient's behavior; otherwise they will cease to engage the patient in mutually reinforcing interactions. Several of the components of CRA, such as communications training and reinforcement reciprocity counseling, are

based on this assumption that increasing the reinforcers in the relationship for both participants will contribute to more enduring good outcomes. However, CRA is not easy to implement, partly because of the requisite that so many reinforcers for the patient be under the control of the therapist/engineer. This is not something that is easy to achieve in most therapeutic efforts (Longabaugh, Wirtz, Clifford, Beattie, & Maisto, 1996).

At the other end of the continuum is the model that focuses on changing the quality of the patient's relationships to those in the network. In this model, dysfunctional and/or unhappy relationships are viewed as a factor in precipitating patient drinking. Focus on decreasing dysfunction or malaise by enhancing the quality of the relationship becomes a goal of the intervention. No study of interventions with the broader network has been identified as having this exclusive goal. Moreover, existing evidence suggests that the pathway from dysfunctional relationships to alcohol abuse is less robust than the pathway from alcohol abuse to dysfunctional relationships (Epstein & McCrady, 1998).

Outside of couples and family therapy efforts, no studies have been identified that explicitly seek to accomplish the dual goals of support for reducing alcohol abuse and relationship enhancement within the broader social network. Longabaugh and colleagues conducted a study that had these two goals, but most of the treatment effort focused on including just one significant other in treatment, most frequently a spouse, so the primary impetus was limited to family intervention (Longabaugh et al., 1995). This is also true for the Community Reinforcement Approach with its underlying philosophy of making the patient's reinforcements conditional upon sobriety while incorporating in treatment mechanisms aimed at increasing the quality of ongoing relationships. It, too, is usually limited to enhancing relationships with one significant other, often times the spouse.

An earlier finding that has not been replicated (Stout, McCrady, Longabaugh, Noel, & Beattie, 1987) is that the impact of randomly assigned, more extensive partner involvement tends to grow over time, whereas for those treated with less emphasis on partner involvement, drinking outcomes decay with time. This finding supports the generic hypothesis that including the network in the treatment can result in an enhanced effect during longer periods of follow-up. Because this effect is not always present, the key research question becomes, what are the necessary and sufficient factors for this enhancement. Two variables hypothesized and observed to affect the impact of the patient's social network on patient outcome are network support for drinking versus abstinence and the patient's investment in the network, measured more generally by the extent to which the relationship is functional, and thus, satisfying to the participants (Longabaugh, Beattie, Noel, Stout, & Malloy, 1993; Longabaugh et al., 1995).

A next generation of therapies involving members of the network in the intervention effort may be gleaned from a Broad Spectrum Therapy (BST) treatment manual recently developed and implemented by Gulliver and Longabaugh (2001). In this approach, the focus and extent of network involvement in treatment is

determined by two criteria: the extent to which the patient's relationship to a segment of the social environment is functional and the extent to which this same segment supports the patient's drinking versus sobriety. The combination of these two criteria yields four possibilities: (1) the relationship is functional and supportive of sobriety, (2) the relationship is functional but supportive of the patient's drinking, (3) the relationship is supportive of the patient's sobriety but dysfunctional, or (4) the relationship is neither functional nor supportive of the patient's sobriety.

Depending on in which limb of the decision tree the patient is classified, the intervention strategies differ. If the relationship is both dysfunctional and supportive of drinking, the therapeutic goal is disengagement. If the relationship is both functional and supportive of sobriety, then no intervention is targeted for this area. If the relationship is supportive of drinking but functional, then the focus is on helping the relationship to be more supportive of sobriety. Last, if the relationship is supportive of sobriety but not functional, the first focus is to improve functioning. If this is not effective, then the focus changes to disengagement. (Depending on whether the patient is cognitively impaired, the specific modalities chosen to accomplish these goals vary).

In the BST approach, the social network is differentiated into patient-spouse relationship (for those who are married), patient relationship to the family of origin and/or procreation, the larger network of friends, and the patient's work relationship (for those having jobs). Each of these components of the network has its own decision tree.

By systematically making these differentiations via rationally imposed decision trees, it is expected that patient outcomes will be enhanced. BST is part of a next generation of therapies because manual-driven treatments will need to become more complex to more closely reflect and use the realities of the patient's social network(s) that affect treatment outcomes.

3. A Summary of Research Priorities

Although the social network is an obvious source of potential influence for affecting the outcomes of those treated for alcohol dependence and abuse, how to make effective use of this network has not been extensively studied. Only for marital and family therapy interventions have there been sustained research programs. Broader use of the patient's social network is just now beginning to receive research attention. Consequently the first research priorities need to address basic questions:

1. Under what set of conditions are specified network interventions effective?
2. Under what set of conditions are specified network interventions contraindicated, either because of client/network resistance to participating in the treatment program or because participation in the intervention leads to poorer outcomes?

3. Under what set of conditions and for whom are network interventions more and less clinically effective than interventions focused exclusively on the identified patient? Is there a dose-response curve?
4. What are the active ingredients of specified network interventions? There is a tremendous gap between theorizing about the active ingredients of treatment and empirical research demonstrating that these putative mechanisms are operative. Mediators of treatment effects need to be tested and identified. Testing the mechanisms through which interventions work has been identified as the highest research priority for alcohol treatment research (Report of a Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Treatment, 1999). A first examination of such a "causal chain analysis" has recently been published by the Project MATCH research group (Longabaugh & Wirtz, 2001).
5. Different network interventions have putatively different strategies (or active ingredients) for success: confrontation, personal support, relationship enhancement, education for influencing sobriety, and systems change. The circumstances under which one and/or the other of these strategies will be more effective need to be tested.
6. What are the characteristics of patients and their network participants that influence the strength of the relationship between network intervention and outcome? (Tests of moderating variables).
7. What are the barriers to using network therapy more widely? Given their demonstrated effectiveness, what are the factors preventing effective dissemination and use?
8. What is the relative cost-effectiveness of network interventions versus alternatives and what are their cost-benefit ratios? Is it really cost-beneficial to terminate network therapies such as behavioral marital therapy?
9. Can therapies involving network participation be integrated with psycho- and pharmacotherapy interventions to enhance the overall effectiveness of interventions for alcohol abuse and dependence?

References

- Azrin, N.H., Sisson, R.W., Meyers, R.J., & Godley, M.D. (1982). Alcoholism treatment by disulfiram and community reinforcement therapy. *Journal of Behavior Therapy and Experimental Psychiatry* 3, 105–112.
- Bacon, S.D. (1973). The process of addiction to alcohol: social aspects. *Quarterly Journal of Studies on Alcohol* 34, 1–27.
- Connors, G.J., Maisto, S.A., & Donovan, D.M. (1996). Conceptualizations of relapse: a summary of psychological and psychobiological models. *Addiction* 91, S5–S13.
- Egelko, S., Galanter, M., Dermatis, H., & DeMaio, C. (1998). Evaluation of a multisystems model for treating perinatal cocaine addiction. *Journal of Substance Abuse Treatment* 15(3), 251–259.
- Epstein, E.E., & McCrady, B.S. (1998). Behavioral couples treatment of alcohol and drug use disorders: Currents status and innovations. *Clinical Psychology Review* 18(6), 689–711.
- Fals-Stewart, W., Birchler, G.R., & O'Farrell, T.J. (1996). Behavioral couples therapy for male substance-abusing patients: Effects on relationship adjustment and drug-using behavior. *Journal of Consulting and Clinical Psychology* 64, 959–972.

- Fals-Stewart, W., O'Farrell, T.J., & Birchler, G.R. (1997). Behavioral couples therapy for male substance abusing patients: A cost outcomes analysis. *Journal of Consulting and Clinical Psychology* 64, 789–802.
- Fals-Stewart, W., O'Farrell, T.J., Feehan, M., Birchler, G.R., Tiller, S., & McFarlin, S.K. (2000). Behavioral couples therapy versus individual-based treatment for male substance-abusing patients. *Journal of Substance Abuse Treatment* 18, 249–254.
- Galanter, M. (1993). Network therapy for addictions: A model for office practice. *American Journal of Psychiatry* 150(1), 28–36.
- Garret, J., Landau, J., Shea, R., Stanton, M.D., Baciewicz, G., & Brinkman-Sull, D. (1998). The ARISE intervention using family and network links to engage addicted persons in treatment. *Journal of Substance Abuse Treatment* 15(4), 333–343.
- Gulliver, S.B., & Longabaugh, R. (2001). A Manual for Broad Spectrum Treatment. Unpublished manual, Center for Alcohol and Addiction Studies, Brown School of Medicine, Providence, Rhode Island.
- Humphreys, K. (1997). Clinicians' referral and matching of substance abuse patients to self-help groups after treatment. *Psychiatric Services* 48(11), 1445–1449.
- Humphreys, K., Moos, R.H., & Finney, J.W. (1996). Life domains, Alcoholics Anonymous, and role incumbency in the 3-year course of problem drinking. *The Journal of Nervous and Mental Disease* 184(8), 475–481.
- Humphreys, K., Moos, R.H., & Cohen, C. (1997). Social and community resources and long-term recovery from treated and untreated alcoholism. *Journal of Studies on Alcohol* 58, 231–238.
- Longabaugh, R., Beattie, M., Noel, N., Stout, R., & Malloy, P. (1993). The effect of social investment on treatment outcome. *Journal of Studies on Alcohol* 54(4), 465–478.
- Longabaugh, R., Wirtz, P.W., Beattie, M.C., Noel, N., & Stout, R. (1995). Matching treatment focus to patient social investment and support: 18-month follow-up results. *Journal of Consulting and Clinical Psychology* 63(2), 296–307.
- Longabaugh, R., Clifford, P.R., & Wirtz, P.W. Behavioral relationship enhancement for alcoholics: Boundaries of effectiveness. Symposium: Marital and spouse involved therapy for alcohol problems: New Directions. *Annual Meeting American Psychological Association*. New York City, NY, August 13, 1995.
- Longabaugh, R., Wirtz, P., Clifford, P., Beattie, M., & Maisto, S. The community reinforcement approach to alcoholism treatment. Symposium: A comparison of community reinforcement and cognitive-behavioral therapy as aftercare for day hospital patients. *Research Society on Alcoholism, Annual Scientific Meeting*. Washington, DC, June 25, 1996.
- Longabaugh, R., Wirtz, P.W., Zweben, A., & Stout, R.L. (1998). Network support for drinking, Alcoholics Anonymous and long-term matching effects. *Addiction* 93(9), 1313–1333.
- Longabaugh, R., & Wirtz, P.W. (eds.) (2001). Project MATCH: Hypotheses, Results, and Causal Chain Analyses. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series. Volume 8.
- McCrady, B.C. (1989). Outcomes of family-involved alcoholism treatment. In M. Galanter (ed.), *Recent Developments in Alcoholism*, Vol. 7. New York: Plenum, pp. 165–182.
- McCrady, B.S., & Epstein, E.E. (1995). Marital therapy in the treatment of alcoholism. In A.S. Gurman & N. Jacobson (eds.), *Clinical Handbook of Marital Therapy*, 2nd ed., New York: Guilford, pp. 369–393.
- McCrady, B.S., Epstein, E.E., & Hirsch, L.S. (1999). Maintaining change after conjoint behavioral alcohol treatment for men: Outcomes at 6 months. *Addiction* 94(8), 1381–1396.
- Meyers, R.J., & Miller, W.R. (eds.) (2001). *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: Cambridge University Press.
- Miller, W.R., Meyers, R.J., & Tonigan, J.S. (1999). Engaging the unmotivated in treatment for alcohol problems: A comparison of three intervention strategies. *Journal of Consulting and Clinical Psychology* 67(5), 688–697.
- Miller, W.R. (ed.) (1999). *Project COMBINE: Combined Behavioral Intervention (CBI) Therapist Manual, Version #3*. New Mexico: University of New Mexico.

- Morgenstern, J., & Longabaugh, R. (2000). Cognitive behavioral therapy for alcohol dependence: A review of evidence for its hypothesized mechanisms of action. *Addiction* 95(10), 1475–1490.
- O'Farrell, T.J. (1986). Marital therapy in the treatment of alcoholism. In N.S. Jacobson & A.S. Gurman (eds.), *Clinical Handbook of Marital Therapy*. New York: Guilford, pp. 513–535.
- O'Farrell, T. (1989). Marital and family therapy in alcoholism treatment. *Journal of Substance Abuse Treatment* 6, 23–29.
- O'Farrell, T.J., Choquette, K.A., & Cutter, H.S.G. (1998). Couples relapse prevention sessions after behavioral marital therapy for male alcoholics: Outcomes during the three years after starting treatment. *Journal of Studies on Alcohol* 59(4), 357–369.
- O'Farrell, T.J., & Fals-Stewart, W. (2000). Behavioral couples therapy for alcoholism and drug abuse. *Journal of Substance Abuse Treatment* 18, 51–54.
- O'Farrell, T.J., Van Houton, V., & Murphy, C.M. (1999). Domestic violence after alcoholism treatment: A two-year longitudinal study. *Journal of Studies on Alcohol* 60, 317–321.
- O'Farrell, T.J., & Murphy, C.M. (1995). Marital violence before and after alcoholism treatment. *Journal of Consulting and Clinical Psychology* 63, 256–262.
- Project MATCH Research Group. (1997a). Matching alcoholism treatments to client heterogeneity: Project MATCH post-treatment drinking outcomes. *Journal of Studies on Alcohol* 58(1), 7–29.
- Project MATCH Research Group. (1997b). Matching alcoholism treatments to client heterogeneity: Tests of the secondary a priori hypotheses. *Addiction* 92(12), 1671–1698.
- Project MATCH Research Group. (1998). Matching alcoholism treatments to client heterogeneity: Treatment main effects and matching effects on drinking during treatment. *Journal of Studies on Alcohol* 59(6), 631–639.
- Smith, I.E., Meyers, R.J., & Miller, W.R. (2001). The community reinforcement approach to the treatment of substance use disorders. *The American Journal of Addictions* 10, 51–59.
- Report of a Subcommittee of the National Advisory Council on Alcohol Abuse and Alcoholism on the Review of the Extramural Research Portfolio for Treatment, November 10–11, 1999.
- Stanton, M.D., & Shadish, W.R. (1997). Outcome, attrition, and family couples treatment for drug abuse: A meta-analysis and review of the controlled, comparative studies. *Psychological Bulletin* 122(2), 170–191.
- Stout, R.L., McCrady, B.S., Longabaugh, R., Noel, N.E., & Beattie, M. (1987). Marital therapy enhances the long-term effectiveness of alcohol treatment. *Alcoholism: Clinical and Experimental Research* 11(2), 213.
- Stout, R.L., Longabaugh, R., Gogineni, A., Rice, C., Beattie, M., & Noel, N.E., Patient-treatment matching: outcome over four years. Presentation at the 30th Annual Association for Advancement of Behavior Therapy Convention. New York City, NY, November, 1996.
- Thomas, E.J., Santa, C.A., Bronson, D., & Oyserman, D. (1987). Unilateral family therapy with spouses of alcoholics. *Journal of Social Service Research* 10, 145–462.
- Thomas, E.J., & Ager, R.D. (1993). Unilateral family therapy with spouses of uncooperative alcohol abusers. In T.G. O'Farrell (ed.), *Treating Alcohol Problems: Marital and Family Interventions*. New York: Guilford, pp. 3–33.

Alcoholics Anonymous and 12-Step Alcoholism Treatment Programs

Keith Humphreys

Abstract. Alcoholics Anonymous (AA) self-help groups are the most commonly accessed component of the de facto system of care for alcohol problems in the United States. Further, AA's concepts and approach have strongly influenced a significant number of professional treatment programs. Nevertheless, only a modest number of longitudinal, comparative outcome studies on AA and on professional 12-step treatment programs have been conducted, which has limited both the certainty and scope of conclusions that can be drawn about these interventions. Research indicates that participation in Alcoholics Anonymous and in 12-step treatment are associated with significant reductions in substance abuse and psychiatric problems. Further, such interventions, it has been found, reduce health care costs over time in naturalistic, quasi-experimental, and experimental studies. Evaluation studies have also begun to illuminate the processes through which self-help groups and 12-step treatment programs exert their effects. To build on this knowledge base, future research should (1) be methodologically flexible and well-matched to its phenomenon of interest, (2) include evaluation of the unique features of self-help organizations, (3) increase representation of African-Americans and women in research samples, and (4) increase statistical power through larger sample sizes and more reliable measurement. Key content areas for future enquiry include further longitudinal evaluation of the outcomes of participation in AA and 12-step treatment (particularly in outpatient samples); better specification of the aspects of AA that influence outcome; and individual-, community-, and health organization-level controlled studies of the health care cost consequences of 12-step interventions.

This chapter reviews evaluation research on Alcoholic Anonymous self-help groups and 12-step alcoholism treatment programs and suggests future directions for scientific work in this area. This is a selective review limited to studies that highlight key findings and unresolved issues in this research area and within the U.S. substance abuse treatment system.

Although "Alcoholics Anonymous" and "12-step treatment" are sometimes used interchangeably, they differ in a number of important respects.

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Alcoholics Anonymous (AA) is a nonprofessional organization that is operated by recovering alcoholic peers, is free of charge to members, and may be attended indefinitely. In contrast, 12-step alcoholism treatment programs are typically licensed/accredited, have paid professional staff, charge fees, and offer services for a defined period. Hence, in this chapter, the term "treatment" will refer only to professionally operated interventions for alcohol problems, and the terms "self-help organization" and "mutual-help organization" will refer only to Alcoholics Anonymous.

1. Nature and Prevalence of Alcoholics Anonymous

Alcoholics Anonymous was founded in 1935 by William Wilson (aka "Bill W") and Robert Smith (aka "Dr. Bob"), both of whom had struggled with alcoholism for many years. During their first meeting in Akron, Ohio, the two men discovered that they could identify with each other and that the process of mutual helping aided them in sustaining sobriety. Drawing ideas from the Oxford Group, William James, Carl Jung, and their own experiences, they developed the concept that recovery from alcoholism is a lifelong process involving spiritual, moral, and physical change. The founders and other early AA members formalized their program of recovery as the "12 steps," which emphasize the importance of admitting inability to control alcohol consumption, learning to humbly accept help, behaving morally, making restitution for past misdeeds, and developing a sense of spiritual serenity. In addition to the steps, AA offers its members a worldwide fellowship of several million people, who support each other in the recovery process.

Today, AA self-help group meetings are the most widely sought source of help for alcohol problems (Weisner, Greenfield, & Room, 1995). Each year, about 3 million problem drinkers attend AA meetings in the United States (Room & Greenfield, 1993). In addition to its major role in the de facto system of care for alcohol dependence, AA has also inspired many new self-help organizations, for example, those devoted to eating disorders, gambling, and smoking.

2. Nature and Prevalence of 12-Step Alcoholism Treatment Programs

More than in any other nation, professional alcoholism treatment programs in the United States have adopted concepts and helping strategies from Alcoholics Anonymous, including using the 12 steps and AA literature to guide psychotherapy, maintaining that alcoholism is an incurable disease, employing "recovering" counselors on staff, and encouraging patients to attend AA meetings and to accept that they are alcoholic. Nevertheless, the common assertion that almost all American treatment programs are "12-step based" is an oversimplification.

For example, many treatment programs that use AA literature and encourage 12-step self-help group involvement nevertheless organize treatment

activities primarily from a cognitive-behavioral rather than from a 12-step perspective (Humphreys, Hamilton, & Moos, 1996). Further, contrary to AA's perspective, many addiction professionals do not consider spiritual change an important aspect of the 12-step model (Morgenstern & McCrady, 1993). Hence, although 12-step ideas are obviously very influential in American treatment programs, professionals modify and emphasize them to widely varying degrees, including ways that depart significantly from AA's approach.

An additional challenge of characterizing "12-step treatment" is the diversity of such interventions (Humphreys, 1999). Some have no purpose other than to encourage 12-step self-help group meeting attendance, whereas others make 12-step ideas a strong focus of ongoing treatment. Further, some deliver 12-step influenced treatment services in the context of a larger medical, professionalized setting, whereas others, for example, "social model" recovery programs (Kaskutas & McLellan, 1998), organize both their services and their setting's entire culture (e.g., staffing requirements, record keeping, operating procedures, intraprogram and community relationships) entirely on AA principles.

3. Evaluations of Community-Based AA Groups

3.1. Evaluation Context

There has never been and probably never will be a controlled prospective study comparing AA versus no intervention or another treatment, for the following reason. Researchers can more easily control access to some interventions (e.g., surgical procedures, novel medications) than others (e.g., exercise, aspirin, self-help groups). As a well-known, widely-available, community-based organization with no admission procedures or fees, AA is easily accessible to anyone, including research participants who have been randomly assigned to a control group in a study of AA's effectiveness. In every controlled, prospective study of AA and/or 12-step treatment in which AA attendance has been monitored in all conditions (e.g., Brandsma, Maultby, & Welsh, 1980), a significant number of individuals who were not assigned to AA have participated in AA on their own, sometimes to a greater extent than individuals assigned to AA by the researcher.

In practical terms, this means that controlled, prospective studies that purport to evaluate AA versus another treatment or no treatment usually evaluate the effect of a higher amount of AA versus a lower amount of AA alone or in combination with a professional treatment. This reality has several implications. First, although we can randomize individuals in AA studies (for example, to participation facilitation or not), we cannot conduct prospective *controlled* trials in the usual sense because we cannot prevent individuals from going to AA. Second, as a field, we have to be careful how we describe the comparative studies that have been conducted. Walsh et al.'s (1991) well-known randomized trial, for example, is often described as "a comparison of AA vs. inpatient treatment" when in fact

every subject in the inpatient treatment condition attended AA meetings. Third, because prospective evaluations usually end up comparing higher versus lower amounts of AA (or a lower amount of AA combined with treatment), they have less sensitivity to AA's potential effects than a "pure" comparison. Hence, under-powered studies focused upon AA effectiveness (e.g., Brandsma et al., 1980) are even harder to interpret than they are in other areas of evaluation research.

3.2. Selected Studies

The meta-analytic research project led by Emrick and Tonigan (Emrick, Tonigan, Montgomery, & Little, 1993; Tonigan, Toscova, & Miller, 1996) assessed AA's effectiveness based on an exhaustive review of the literature. Their general conclusion was that AA involvement was associated with reduced drinking and drinking-related problems, and, to a more modest extent, with better psychological and social functioning. Effect sizes for AA, when calculable, ranged from what Cohen (1992) terms "small" to "medium." However, as most of the AA research underlying these conclusions was correlational, the observed relationship of AA participation to better outcome may be a function of self-selection. In support of this conjecture, some studies (e.g., Morgenstern, Labouvie, McCrady, Kahler, & Frey, 1997) have found that AA attenders have greater prior motivation to reduce alcohol consumption (e.g., they report an abstinence goal) than nonattenders, a selection artifact that could lead to overestimation of AA's effectiveness in some correlational studies. Yet other studies point to the reverse type of selection bias (i.e., bias that understates rather than overstates AA's effectiveness): AA appears to attract problem drinkers who have more severe alcohol problems (Emrick et al., 1993). Hence, although individual correlational studies of AA may have significant selection bias in one direction or the other, there is no reason to believe that all such studies combined (upon which the meta-analytic work of Emrick, Tonigan and colleagues rests) have a selection bias in a consistent direction.

Of course, longitudinal studies with comparison groups allow stronger conclusions. Ditman and colleagues (1967) randomized (through judge's order) "chronic drunk offenders" to either five AA meetings ($n = 86$), an alcoholism clinic ($n = 82$), or a no intervention control condition ($n = 73$). During the ensuing year, offenders in the three conditions did not differ in rates of rearrest. Unfortunately, this study gathered no data on alcohol consumption or psychological functioning, did not describe whether individuals in the control condition voluntarily received any treatment or attended AA, and focused on a very low "dose" of AA participation.

A more sophisticated longitudinal study examined blue-collar workers whose alcohol problems had resulted in their coming into contact with an employee assistance program (Walsh, Hingson, Merrigan, Levenson, Cupples, Heeren, Coffman, Becker, Barker, Hamilton, McGuire, & Kelly, 1991). In the two experimental conditions of primary interest here, 73 employees were randomly assigned to compulsory inpatient treatment combined with concurrent

and posttreatment AA, whereas 83 others were assigned to attend community-based AA groups only. Compliance with assigned condition, substance use, and job performance were closely monitored throughout the study. During a 2-year period, both groups showed similar and substantial improvement on 12 job-related performance measures. However, the inpatient treatment plus AA condition was superior on several substance abuse-related outcomes. Individuals assigned to the AA-only condition improved on substance use measures in absolute terms but had more frequent relapses during the course of the study than the inpatient treatment plus AA group. At the same time, the AA-only group had 10% lower health care costs during the course of study, so AA alone was less costly, even though it was less effective in purely clinical terms.

In both of these randomized trials, subjects were closely monitored and faced predictable and severe consequences (e.g., job loss or imprisonment) for (1) noncompliance with their assigned treatment regimen and (2) continued drinking. Hence, the results of these studies may not generalize to help-seeking individuals who are subjected to less consistent pressure and monitoring (e.g., occasional criticism about drinking from family members, periodic threats of divorce by a spouse). An initial concern about the Walsh study is that its primary comparison lacks substantial health care policy relevance, because, in the real world, quite different populations of drinkers pursue AA alone versus inpatient treatment combined with AA (Timko, Finney, Moos, Moos, & Steinbaum, 1993).

To evaluate the effects of AA with greater ecological validity, Humphreys and Moos (1996) identified a sample of alcohol-abusing individuals who initially sought AA ($n = 135$) or outpatient treatment ($n = 66$). Despite not being randomly assigned, the two groups were not significantly different at baseline on most prognostic measures, including prior treatment experience (none had any) and current help-seeking/motivation (all were seeking help). At 1- and 3-year follow-ups, both groups improved substantially (e.g., decreased ethanol consumption and alcohol dependence symptoms by about 70%). The amount of improvement experienced by AA participants was comparable to that experienced by individuals who received outpatient treatment. As with the Walsh et al. (1991) study, alcohol-related health care costs differed significantly between conditions; the group that initially attended AA had 45% (\$1,826 per person) lower costs during the course of the study than the group that initially selected outpatient treatment.

A few studies have attempted to specify the change processes involved in community-based AA participation. In a study of 100 patients (42% female) previously treated in private hospital programs, Morgenstern and colleagues (1997) found that AA involvement predicted increases in active coping responses, commitment to abstinence, self-efficacy, and appraisal of substance abuse as a source of harm. These changes, in turn, predicted decreased substance use. A study with a quite different sample (2,337 male VA patients) also found that 12-step mutual-help groups' effect on substance use was mediated

by increases in active coping responses and enhancements to friendship networks (Humphreys, Mankowski, Moos, & Finney, 1999).

Given AA's emphasis on spiritual and moral change, these mediational results on coping responses, self-efficacy, and the like may be surprising and seem to "fit better" with theories of change from professional psychosocial treatments like cognitive-behavioral therapy. Although the AA fellowship puts its program in a moral and spiritual framework, experienced AA members and AA texts offer extensive practical advice to newcomers such as thinking of reasons for not drinking, focusing on the positive aspects of sobriety, avoiding drinking companions, monitoring thoughts that may precipitate relapse, and finding alternatives to drinking when under stress. Hence, even though some AA members do experience dramatic changes in their spiritual life, more prosaic change processes are also at work in the organization.

In summarizing the above findings, AA's cherished standard of humility should be borne in mind. Although in recent years evaluation research on community-based AA groups has improved in terms of using longitudinal designs, larger samples, and multidimensional measures of AA involvement, the body of quality research in this area is not large. Accordingly, the following conclusions are preliminary:

- Individuals participating in AA will, on average, reduce their substance abuse and psychiatric problems. Effect sizes for AA participation generally range from "small" to "medium" and are probably roughly comparable to those associated with outpatient treatment.
- Under conditions of close monitoring and substantial coercion, AA combined with inpatient treatment leads to fewer relapses than AA alone, and, being ordered to AA does not reduce likelihood of future arrest.
- AA involvement predicts reduced alcohol-related health care expenditures.
- Enhanced coping and commitment to abstinence, increased self-efficacy and appraisal of substances as harmful, and improved friendship networks are part of the causal process through which AA involvement affects drinking behavior.

4. Evaluation Research on 12-Step Oriented Professional Treatment Programs

4.1. Evaluation Context

Many efforts have been made to evaluate 12-step oriented treatments, but not all of them are useful for present purposes. First, researchers do not always describe the content and philosophy of the treatments they evaluate. Hence, some evaluations of 12-step oriented care are not clearly identified as such (e.g., presumably, some comparative studies of different modalities of alcohol treatment have included 12-step programs). Second, there is a large clinical literature

in which 12-step treatment is clearly being examined, but evidence of effectiveness in these writings is typically inferred from cross-sectional impressions of single patients or groups of patients. Third, although some 12-step treatment programs have conducted clinical outcome evaluations, the results of such efforts are often hard to obtain and evaluate. For example, Laundergan's (1993) review of effectiveness studies conducted in "Minnesota Model" treatment programs included only one peer-reviewed journal article; all other work appeared within in-house reports, manuals, books, and the like. Given this context, the focus will be restricted here to recent studies in which (1) it was clear that at least one treatment had a 12-step orientation, (2) the design was longitudinal and included comparison/control groups, and (3) results were published in peer-reviewed journals.

4.2. Selected Studies

Project MATCH (1997, 1998) compared cognitive-behavioral therapy and motivational enhancement therapy with 12-step facilitation counseling (TSF) in a randomized clinical trial of 1726 patients (inpatient arm = 774, outpatient arm = 952) diagnosed with alcohol abuse or dependence. TSF was a form of professional, one-on-one counseling explicitly designed to work synergistically with Alcoholics Anonymous and other 12-step groups. Consistent with the philosophy of AA, TSF therapists presented alcohol dependence as a disease with spiritual, emotional, and physical components and emphasized that it could be arrested but not cured through permanent abstinence from alcohol. They also strongly encouraged patients to attend AA meetings and to keep a journal describing their reactions to AA.

For present purposes, discussion of Project MATCH's many findings can be profitably restricted to the general pattern of outcome differences between TSF therapy and the other two treatments. At both 1- and 3-year follow-ups, patients in all three conditions improved significantly on alcohol-related (e.g., number of drinks per day), psychiatric (e.g., depressive symptoms), and life functioning (e.g., days of employment) outcomes. Overall, each treatment produced similar changes in patients, with two exceptions. First, as intended, TSF therapy was significantly more successful than the other two treatments at increasing AA involvement, as indexed by such behaviors as attending meetings, having and being a sponsor, working the 12 steps, and considering oneself an AA member (Tonigan, Connors, & Miller, *in press*). Second, at each follow-up, TSF therapy produced significantly higher rates of abstinence. This result is consistent with the goals of TSF therapy and with AA, neither of which view moderate drinking as an acceptable goal for alcohol-dependent individuals.

Project MATCH (1997) was, of course, also intended to evaluate whether various patient characteristics interacted with treatment characteristics to affect outcome. The primary matching hypotheses were not supported. However, one interesting, unexpected interaction was identified. Among outpatients with low psychopathology, TSF patients had more days of abstinence

than cognitive-behavioral therapy patients. Among high psychopathology patients, no outcome differences were found.

A substantial proportion of Project MATCH participants who received motivational enhancement or cognitive-behavioral therapy attended AA on their own, even though this was not a special focus of treatment. Other than a surprising *positive* relationship between AA attendance and drinking intensity in the cognitive-behavioral outpatient arm at 6 months (Tonigan et al., *in press*), patients in both study arms benefited from AA, even if they had not been originally assigned to TSF.

Concurrent with Project MATCH, The Department of Veterans Affairs (VA) conducted a nationwide treatment evaluation with male substance abuse inpatients who provided data at baseline, discharge, and 1-year follow-up (Moos, Finney, Ouimette, & Suchinsky, 1999). Discussion of the many findings of this complex study will be restricted here to selected results for the subset of inpatients that received treatment in programs that strongly exemplified either a 12-step approach or a cognitive-behavioral approach.

The five 12-step-oriented inpatient programs in the VA study emphasized treatment activities such as attending 12-step group meetings in the community and on-site, working the 12 steps, reading the "Big Book" and other literature of AA/NA, and accepting the identity of alcoholic/addict. Staff members in these programs strongly endorsed the disease model of addiction and reported spending most of their time on 12-step treatment activities. The five cognitive-behavioral treatment programs required participation in relapse prevention groups, cognitive skills training, and cognitive-behavioral group therapy. Analysis of program schedules showed that cognitive-behavioral programs spent less than 5% of treatment time on activities based on 12-step principles.

A total of 2045 men was treated in either a 12-step-oriented ($n = 897$) or a cognitive-behavioral ($n = 1148$) inpatient program and then followed-up 1 year after discharge. Almost all were alcohol-dependent, half were also drug-dependent, and one-fifth had a comorbid Axis I psychiatric disorder.

Interestingly, the outcome results of the VA study were quite similar to those of Project MATCH. In both 12-step-oriented and cognitive-behavioral treatment, patients experienced substantial reductions in substance use, substance abuse-related problems, psychological problems, criminal behavior, and unemployment (Moos et al., 1999). Further, the overall results indicated that the different treatments were comparably effective; the only notable exception again was that 12-step-oriented treatment had an advantage in promoting complete abstinence. For example, at 1-year follow-up, rates of abstinence from drugs and alcohol for the past 3 months were 45% for patients treated in 12-step-oriented programs versus 36% for patients treated in cognitive-behavioral programs.

At baseline, there were no differences in the prior level of self-help group involvement of patients entering 12-step and cognitive-behavioral treatment programs. One year after treatment, many patients in both conditions were attending AA/NA, but involvement rates were substantially higher among patients previously treated in 12-step-oriented programs (Humphreys, 1999).

Like Project MATCH's 6-month follow-up of patients initially assigned to cognitive-behavioral psychotherapy, the VA study also found some evidence suggesting that 12-step self-help group involvement may be more helpful when patients have received 12-step-oriented treatment than when they have received cognitive-behavioral treatment. Among patients receiving 12-step-oriented treatment, abstinence rates 1 year after treatment increased from 19% for patients less involved with self-help groups after treatment to 75% for more involved patients. Among patients receiving cognitive-behavioral treatment, abstinence rates increased from 25% for patients less involved in self-help groups after treatment to only 65% for highly involved patients. This statistically significant difference indicates that 12-step self-help group involvement benefited patients treated in 12-step programs more than patients treated in cognitive-behavioral programs (Humphreys, Huebsch, Moos, & Finney, 1999).

Last, the VA study attempted to identify client by treatment interactions based on a priori matching hypotheses. As with Project MATCH, the findings of the VA study provided almost no support for the value of treatment matching (Ouimette, Finney, Gima, & Moos, 1999).

A final important study examined heterosexual couples who were receiving alcohol-related behavioral couples therapy (McCrady, Epstein, & Hirsch, 1999). Couples were randomly assigned to receive only couples therapy ($n = 30$) or to have it supplemented with relapse prevention training ($n = 31$) or with a TSF-style intervention ($n = 29$). The TSF-style intervention introduced patients to AA and Al-Anon philosophy and methods, helped patients to identify accessible meetings and to set goals for attendance, encouraged patients to get a sponsor and work the 12 steps, and assigned AA/Al-Anon-related homework.

During treatment, the TSF-style intervention was highly successful in increasing attendance at 12-step self-help groups. However, 6-month outcomes were roughly comparable across conditions (e.g., about 50% of patients were abstinent or engaged in nonproblem drinking), and what differences there were favored the two purely behavioral conditions that did not include TSF. In other words, echoing other findings just reviewed, supplementing cognitive-behavioral marital therapy with 12-step self-help group involvement did not enhance the effectiveness of the treatment.

As with community-based AA, researchers have attempted to identify mediational factors within 12-step treatment programs. Morgenstern, Kahler, Frey, and Labouvie (1996) found that 12-step treatment led most substance abuse patients to engage in many 12-step-related behaviors immediately following treatment (e.g., reading 12-step literature, attending meetings, praying/meditating). Using treatment discharge data, Finney and colleagues (1998) replicated this finding but also found that 12-step treatment produced changes in putatively cognitive-behavioral proximal outcomes as well (e.g., decreased positive perceptions of substance use, greater self-efficacy). Like the mediational studies of community-based AA groups described earlier, these results suggest that 12-step and non-12-step interventions share some change processes, which helps explain why their overall outcomes are fairly similar.

Both of the above studies examined whether these end-of-treatment changes in proximal outcomes predicted distal substance abuse outcomes. Although some relationships were identified, they were of very modest magnitude compared to those found in the community-based AA studies discussed earlier. This difference is probably due to the fact that 12-step treatment has usually been over for some time before final outcome assessments are conducted, whereas individual AA involvement may continue through an entire follow-up window.

Finally, again similar to the studies of community based AA groups, some treatment-based studies provide strong evidence of health care cost reductions attributable to a 12-step approach. In a randomized clinical trial with 235 patients, Galanter (1984; Galanter, Castaneda, & Salamon, 1987) compared an outpatient treatment unit based on self-help principles (e.g., high patient involvement and peer support) with an outpatient unit in the same hospital that had less self-help emphasis and twice as many professional staff members. Despite the substantially lower personnel costs of the self-help-oriented treatment unit, its clinical outcomes were similar or superior to those produced by the more professionalized treatment program. In a quasi-experimental study of 1774 patients in 10 treatment programs, Humphreys and Moos (2001) found that, relative to cognitive-behavioral programs, in programs that strongly emphasized the value of AA/NA attendance, patients relied more on AA/NA and less on further professional treatment after discharge. This reduced inpatient and outpatient care costs by 39% in the year following 12-step-oriented treatment (about \$5000/patient) with no adverse effect on 1-year outcomes. These findings, which parallel those of similar studies in the psychiatric treatment field (e.g., Gordon, Edmunson, Bedell, & Goldstein, 1979), make a strong case that self-help principles and organizations can enhance the cost-effectiveness of professional treatment.

To summarize, a number of conclusions can be drawn about 12-step treatment. This can be done with more confidence than in the summary of findings on community-based AA evaluations because treatment studies are more numerous and because certain research designs are easier to implement in 12-step treatment programs than in community-based AA groups:

- Professional interventions can substantially increase substance abuse patients' attendance at 12-step self-help group meetings.
- Twelve-step-oriented treatments generally produce outcomes comparable to those of cognitive-behavioral treatments and have a slight advantage on abstinence outcomes.
- Self-help-oriented treatments are more cost-effective than otherwise similar non-self-help-oriented treatments.
- Cognitive-behavioral and 12-step treatments share some change processes. At the same time, combining cognitive-behavioral treatments with AA/NA affiliation may be less helpful to patients than combining 12-step treatment with AA/NA affiliation, perhaps because the consistency of the

overarching philosophy facilitates patients' learning of new ways of thinking and behaving.

- Identifying patient–treatment matches for 12-step and other treatments is very difficult, even in large, well-designed studies. Hence, patient–treatment matching effects may be too small or unstable to be of substantial use in real-world clinical practice.

5. Potential Future Research Directions

This section presents recommendations for future research on alcohol-related self-help groups and self-help influenced treatments. First, four crosscutting process issues relevant to all future investigations will be described. Then, four specific content areas will be outlined in which future research could be focused.

5.1. *Process Recommendations*

5.1.1. Be Methodologically Flexible. Few researchers would dispute that AA is an important feature of the United States' de facto system of intervention for alcohol problems, yet relatively few published studies (and even fewer grant proposals) focus on AA. This stems in part from familiar research methods developed to study treatments (e.g., exclusion criteria, manualized interventions) at times being hard to implement, or simply inappropriate, in research on an anonymous, peer-run, nonstandardized, spiritually based, community-based, self-help organization.

Given this situation, it may be helpful for those who would study AA or evaluate AA research to remember that no research method is valuable *in itself*. Rather, particular research methods are valuable because of the way they help scientists understand particular phenomenon in context. This implies that methodological flexibility may be necessary for AA research, for example, reaching beyond the traditions of randomized clinical trials to the traditions of qualitative sociology, epidemiology, and applied program evaluation.

5.1.2. Include Evaluation of the Unique Features of Alcohol Mutual-Help Organizations. Although mutual-help organizations share some goals and characteristics with treatment programs, they also have some unique features. For example, they are social organizations that provide participants long-term opportunities for friendship, recreation, and a sense of belonging. For those individuals who participate in them for a period of years, mutual-help organizations serve as communities that sustain meaning and prosocial values and shape identity and a world view. Further, many self-help organizations (e.g., AA, Alcoholics Victorious) operate primarily from a spiritual framework and attempt to foster spiritual growth in their members.

It is probably natural to generalize from the known to the unknown when trying to understand new things. Hence, researchers attempting to evaluate

self-help organizations may decide which variables to emphasize, measure, and model based on their experience in evaluating professional treatment programs. Although this can be a useful starting point, future evaluations of self-help groups should broaden their scope to include constructs that are more important in self-help organizations than they are in most treatments, such as spirituality, friendship-making, sense of community, long-term values reorientation, and the other areas just discussed. Such constructs can be examined as predictors of participation in mutual-help groups, as mediators of the effect of mutual help group participation on alcohol use, and as important outcomes in themselves.

5.1.3. Increase Representation of African-Americans and Women in Research Samples. Studies of AA and of 12-step influenced treatments have not fully reflected the diversity of participants in their samples (Emrick et al., 1993). For both ethical and scientific reasons, this is an important problem to rectify across future research projects. One concrete strategy for increasing the diversity of samples would be to encourage studies of the combined effects of AA and NA (which African-American mutual-help group members often coattend) and AA and Al-Anon (which female mutual-help group members often coattend).

5.1.4. Increase Statistical Power through Larger Sample Sizes and More Reliable Measurement. Tonigan and colleagues (1996) found that many studies of AA have been underpowered, resulting in a high likelihood of Type II error. In combination with the near impossibility of conducting pure comparisons of AA versus no AA (another source of Type II error, as described earlier in this chapter), Tonigan's finding underscores the need to substantially increase the statistical power of future research on alcohol-related self-help groups.

Statistical power can be enhanced by increasing sample sizes and by employing more reliable measures. Fortunately, in recent years, a number of reliable, multidimensional measures of 12-step group involvement have been developed (e.g., Morgenstern et al., 1996). Such measures should completely supplant unreliable single-item measures (e.g., number of AA meetings/TSF sessions attended) in future research on 12-step interventions.

5.2. Specific Content Areas for Focused Enquiry

5.2.1. Longitudinal Evaluations of the Effect of AA and 12-Step Treatments on Alcohol-Related and Psychosocial Outcomes. Quite simply, there are disappointingly few straightforward, well-designed evaluations of the way these interventions affect alcohol-related and psychosocial outcomes. Expanding on the base of comparative/controlled, longitudinal outcome research should therefore be a major priority. To increase their policy relevance, such studies should reflect the nature of the current formal and informal care system for alcohol problems, that is, primary attention should be devoted to evaluating

community-based self-help organizations and outpatient and residential 12-step treatment programs (versus hospital-based inpatient programs such as those examined in the Walsh et al. and VA study). Recently funded studies evaluating the effectiveness of two forms of outpatient TSF counseling (PI: Dr. Kimberly Walitzer), of "social model" day treatment programs (PI: Dr. Lee Ann Kaskutas), of peer-managed Oxford Houses (PI: Dr. Leonard Jason), and of Double Trouble in Recovery 12-step self-help groups (PI: Dr. Steven Magura) are important steps in this direction.

5.2.2. Mediational Studies. Mediational studies go beyond simple issues of global effectiveness (i.e., "Does the intervention work?") to examine *how* an intervention succeeds or fails to produce an intended outcome (Finney, 1995). More research along this line, which could be embedded in the outcome evaluations described above, could more fully explicate which features of AA and 12-step treatment are central in the change process. Building on the work of Morgenstern and colleagues (1996, 1997), it would also be useful to specify the intraindividual change processes (e.g., enhanced self-efficacy) that ultimately lead to reduced substance use by mutual-help group members and by patients in 12-step treatment programs. Better understanding of such mediational links may help improve the process of treatment as well as spur the development of more sophisticated conceptual models of recovery from substance abuse.

One potentially important process variable has yet to be carefully examined and thus deserves special mention: sponsorship. There are probably at least 100,000 AA sponsors in the United States, providing support, advice, and guidance to alcohol-dependent individuals. Yet researchers know virtually nothing about what they actually do and whether or not it is helpful. Examination of how having a sponsor, being a sponsor, and sponsor–spousee interactions influence the recovery process thus would seem a crucial topic for future mediational research.

5.2.3. Studies of Professional Treatment–Self-Help Group Combinations. A significant proportion of individuals who begin participating in self-help groups have just completed or are still receiving professional treatment services. Hence, evaluating the effectiveness of different combinations of professional treatment and self-help group participation is a research priority with high clinical and policy relevance. Some of the research reviewed herein suggests that consistency of approach between treatment and self-help groups may enhance patients' engagement in care and alcohol-related outcomes. Accordingly, it may be useful to conduct clinical trials in which alcohol patients' treatment and self-help group involvement are concordant (e.g., both 12-step, both cognitive-behavioral) versus discordant (e.g., one 12-step, the other cognitive-behavioral). Outcome data from such trials, which would necessarily include study of cognitive-behavioral self-help organizations like SMART Recovery and Moderation Management, could inform practice guidelines on care coordination across the professional and voluntary helping sectors.

Another key research question is how extensive professional intervention must be to propel a patient into lasting self-help group affiliation. Clearly, TSF interventions that engage patients for a significant period (e.g., 10–12 sessions) can sharply increase the likelihood that patients will attend AA. However, many patients in primary care and addiction treatment are not seen for extended periods, so a briefer version of TSF interventions would be more clinically useful (Humphreys, 1999). Sisson and Mallams' (1981) one-session TSF intervention is a promising beginning worthy of more evaluation.

5.2.4. Studies of the Health Care Cost Consequences of Self-Help Group Participation.

Given the reduced fiscal resources available for substance abuse treatment, the cost-effectiveness and health care cost offsets of self-help groups and self-help-influenced treatments warrant further investigation. Cost-related questions could be embedded in outcome studies of the sorts described above. For example, a randomized trial of the effects of a brief TSF intervention on alcohol outpatients could monitor ongoing health care costs in addition to alcohol-related outcomes and 12-step group participation. Such studies will be most useful if they examine potential mediating processes (e.g., reducing loneliness and unreasonable anxiety) through which self-help group involvement can lower health care use without compromising health. Presumably, some of these techniques and processes could be generalized to professional health care settings where they could promote more appropriate use of services.

The health care cost consequences of self-help-oriented interventions could be examined at the level of individual alcohol patients and also at the community and health policy levels. For example, in a small group of experimental communities, media campaigns and self-help clearinghouses could be employed to increase participation in alcohol self-help groups. Alcohol-related health care use over time in these communities could then be compared with those of control communities. At the health policy level, evaluations could be conducted within health maintenance or preferred provider organizations, for example, by randomly assigning half of an insured population an extra benefit of an "alcohol use checkup" followed by a self-help group facilitation intervention, where appropriate. In addition to assessing health outcomes, such studies could examine whether streaming newly identified problem drinkers into self-help groups reduces subsequent use of professional alcohol treatment services.

References

- Brandsma, J.M., Maultby, M.C., & Welsh, R.J. (1980). *Outpatient Treatment of Alcoholism: A Review and Comparative Study*. Baltimore, MD: University Park Press.
- Cohen, J. (1992). A power primer. *Psychological Bulletin* 112, 155–159.
- Ditman, K.S., Crawford, G.G., Forgy, E.W., Moskowitz, H., & MacAndrew, C. (1967). A controlled experiment on the use of court probation for drunk arrests. *American Journal of Psychiatry* 124, 64–67.

- Emric k C.D., Tonigan, J.S., Montgomery, H., & Little, L. (1993). Alcoholics Anonymous: What is currently known? In B.S. McCrady, & W.R. Miller (eds.), *Research on Alcoholics Anonymous: Opportunities and Alternatives*. New Brunswick, NJ: Rutgers Center of Alcohol Studies, pp. 41–76.
- Finney, J.W. (1995). Enhancing substance abuse treatment evaluations: Examining mediators and moderators of treatment effects. *Journal of Substance Abuse* 7, 135–150.
- Finney, J.W., Noyes, C.A., Coutts, A.I., & Moos, R.H. (1998). Evaluating substance abuse treatment process models: I. Changes on proximal outcome variables during 12-step and cognitive-behavioral treatment. *Journal of Studies on Alcohol* 59, 371–380.
- Galanter, M. (1984). Self-help large group therapy for alcoholism: A controlled study. *Alcoholism: Clinical and Experimental Research* 8, 16–23.
- Galanter, M., Castaneda, R., & Salamon, I. (1987). Institutional self-help therapy for alcoholism: Clinical outcome. *Alcoholism: Clinical and Experimental Research* 11, 424–429.
- Gordon, R.E., Edmunson, E.D., Bedell, J., & Goldstein, N. (1979). Reducing rehospitalization of state mental patients. *Journal of the Florida Medical Association* 66, 927–933.
- Humphreys, K. (1999). Professional interventions that facilitate 12-step self-help group involvement. *Alcohol Health and Research World* 23, 93–98.
- Humphreys, K., & Moos, R. (1996). Reduced substance abuse-related health care costs among voluntary participants in Alcoholics Anonymous. *Psychiatric Services* 47, 709–713.
- Humphreys, K., & Moos, R. (2001). Can encouraging substance abuse inpatients to participate in self-help groups reduce demand for health care?: A quasi-experimental study. *Alcoholism: Clinical and Experimental Research* 25, 711–716.
- Humphreys, K., Hamilton, E.G., & Moos, R.H. (1996). *Substance Abuse Treatment in the Department of Veterans Affairs: System Structure, Patients and Treatment Activities*. Palo Alto, CA: Center for Health Care Evaluation.
- Humphreys, K., Huebsch, P.D., Moos, R.H., & Finney, J.W. (1999). A comparative evaluation of substance abuse treatment: V. Treatment can enhance the effectiveness of self-help groups. *Alcoholism: Clinical and Experimental Research* 23, 558–563.
- Humphreys, K., Mankowski, E., Moos, R.H., & Finney, J.W. (1999). Do enhanced friendship networks and active coping mediate the effect of self-help groups on substance use? *Annals of Behavioral Medicine* 21, 54–60.
- Kaskutas, L.A., & McLellan, A.T. (1998). The social model approach to substance abuse recovery (Special Issue). *Journal of Substance Abuse Treatment* 15(1), 5–74.
- Lauderger, J.C. (1993). How could studies of Alcoholics Anonymous be designed?: Evaluation within treatment contexts. In B.S. McCrady & W.R. Miller (eds.), *Research on Alcoholics Anonymous: Opportunities and alternatives*. New Brunswick, NJ: Rutgers Center of Alcohol Studies, pp. 321–338.
- McCrady, B.S., Epstein, E.E., & Hirsch, L.S. (1999). Maintaining change after conjoint behavioral alcohol treatment for men: Outcomes at six months. *Addiction* 94, 1381–1396.
- Moos, R.H., Finney, J.W., Ouimette, P.C., & Suchinsky, R.T. (1999). A comparative evaluation of substance abuse treatment: I. Treatment orientation, amount of care, and 1-year outcomes. *Alcoholism: Clinical and Experimental Research* 23, 529–536.
- Morgenstern, J., & McCrady, B.S. (1993). Cognitive processes and change in disease model treatment. In B.S. McCrady and W.R. Miller (eds.), *Research on Alcoholics Anonymous: Opportunities and Alternatives*. New Brunswick, NJ: Rutgers Center of Alcohol Studies, pp. 153–164.
- Morgenstern, J., Kahler, C.W., Frey, R.M., & Labouvie, E. (1996). Modeling therapeutic response to 12-step treatment: Optimal responders, nonresponders, and partial responders. *Journal of Substance Abuse* 8, 45–59.
- Morgenstern, J., Labouvie, E., McCrady, B.S., Kahler, C.W., & Frey, R.M. (1997). Affiliation with Alcoholics Anonymous following treatment: A study of its therapeutic effects and mechanisms of action. *Journal of Consulting and Clinical Psychology* 65, 768–777.
- Ouimette, P.C., Finney, J.W., Gima, K., & Moos, R.H. (1999). A comparative evaluation of substance abuse treatment. III. Examining mechanism, underlying patient-treatment matching hypotheses for 12-step and cognitive-behavioral treatments for substance abuse. *Alcoholism: Clinical and Experimental Research* 23, 545–551.

- Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–29.
- Project MATCH Research Group. (1998). Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcoholism: Clinical and Experimental Research* 22, 1300–1311.
- Room, R., & Greenfield, T. (1993). Alcoholics Anonymous, other 12-step movements and psychotherapy in the US population, 1990. *Addiction* 88, 555–562.
- Sisson, R.W., & Mallams, J.H. (1981). The use of systematic encouragement and community access procedures to increase attendance at Alcoholics Anonymous and A1-Anon meetings. *American Journal of Drug and Alcohol Abuse* 8, 371–376.
- Timko, C., Finney, J.W., Moos, R.H., Moos, B.S., & Steinbaum, D.P. (1993). The process of treatment selection among previously untreated help-seeking problem drinkers. *Journal of Substance Abuse* 5, 203–220.
- Tonigan, J.S., Toscova, R., & Miller, W.R. (1996). Meta-analysis of the literature on Alcoholics Anonymous: Sample and study characteristics moderate findings. *Journal of Studies on Alcohol* 57, 65–72.
- Tonigan, J.S., Connors, G.J., & Miller, W.R. (in press). Participation and involvement in Alcoholics Anonymous. In T. Babor & F. DelBoca (eds.), *Treatment Matching in Alcoholism*. London: Cambridge University Press.
- Walsh, D., Hingson, R., Merrigan, D., Levenson, S., Cupples, L., Heeren, T., Coffman, G., Becker, C., Barker, T., Hamilton, S., McGuire, T., & Kelly, C. (1991). A randomized trial of treatment options for alcohol-abusing workers. *New England Journal of Medicine* 325, 775–782.
- Weisner, C., Greenfield, T., & Room, R. (1995). Trends in the treatment of alcohol problems in the U.S. general population, 1979 through 1990. *American Journal of Public Health* 85, 55–60.

Behavioral and Cognitive-Behavioral Treatments for Alcoholism

Research Opportunities

Ronald M. Kadden

During the past half-century, behavior theory has been expanded beyond its behaviorist beginnings into the cognitive-behavioral realm and has been adapted to treating a wide range of human problems. As applied to alcoholism, it provides a theoretical framework for understanding the etiology and persistence of pathological drinking and a conceptual basis for developing clinical interventions to treat the disorder. Its basic assumption is that pathological drinking is to a large extent learned behavior, and therefore learning-based interventions will be effective in changing it (Rotgers, 1996). From this perspective, treatment involves behavioral assessment, a functional analysis to determine the role of drinking in each individual's life, a learning-based intervention (variants of which are covered in this chapter), and practice of new behaviors in real-life settings.

In conducting this review of research on learning-based interventions, both "behavioral" and "cognitive-behavioral" studies have been included. "Behavioral" approaches emphasize the external antecedents and consequences that affect behavior, without making reference to mediational states, cognitions, or other private events. "Cognitive-behavioral" approaches include cognitive processes and emotions among the factors that may precipitate or maintain behavior and use both behavioral and cognitive methods to promote behavioral change (Kazdin, 1982).

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The review is not exhaustive. Other behavioral treatment methods could also have been addressed (e.g., aversive conditioning), and one (Community Reinforcement Approach) is covered in its own chapter elsewhere in this volume. The selection represents the author's judgment, based on several meta-analyses (Holder, Longabaugh, Miller, & Rubonis, 1991; Miller et al., 1995; Finney & Monahan, 1996), as to which methods have been the most successful in clinical trials. The following topics are covered: cue exposure, contingency management, coping skills training, relapse prevention, and behavioral marital therapy. The coverage of each topic includes a brief status report, followed by sections identifying gaps in knowledge and possible directions for future research, based on recommendations in the literature and by this author. In addition to outcome research, the review also includes some studies of process and mechanisms of change.

1. Cue Exposure

One behavioral model of alcohol dependence is predicated on the associative learning principle that neutral stimuli which regularly precede drinking can, with repeated pairings, become capable of eliciting conditioned responses that may prompt drinking (Niaura, Rohsenow, Binkoff, Monti, Pedraza, & Abrams, 1988). In its purest form, this model is based entirely on Pavlovian (respondent) conditioning, in which conditioned stimuli directly elicit drinking. In another variant, a two-stage process is invoked in which conditioned stimuli elicit interoceptive responses which serve as discriminative stimuli that set the occasion for, and increase the likelihood of, drinking (Pomerleau, Fertig, Baker, & Cooney, 1983). Both versions of the model entail assumptions about alcoholics' reactivity to environmental cues and the relationship of that reactivity to subsequent drinking. Researchers have examined the relationship of drinking cues to behavioral, physiological, and cognitive responses; the relationship of those responses to subsequent drinking; and the clinical efficacy of cue exposure as a treatment procedure (Drummond, Cooper, & Glautier, 1990; Rohsenow, Niaura, Childress, Abrams, & Monti, 1991).

1.1. *Gaps in Knowledge*

In a number of studies, alcohol-related cues have not been potent as elicitors of conditioned responses. Rohsenow et al. (1992) found that as many as one-third of alcoholics did not report an increased urge to drink in a laboratory-based cue exposure situation. Monti et al. (1993a) found that 30% of alcoholics did not report an increased urge to drink and 35% did not increase salivation in response to the sight of alcohol. In another study, as many as 40–50% of alcoholics exhibited no elicited response to alcohol cues (Litt, Cooney, Kadden, & Gaupp, 1990). Efforts to enhance the potency of the cue-exposure procedure have included adding emotional arousal to the stimulus situation, but results

have been mixed. One study found an increase in a cue-elicited urge to drink following induction of a negative mood (Rubonis, Colby, Monti, Rohsenow, Gulliver, & Sirota, 1994), although salivary responding to the cue was not enhanced. Another study found that emotional arousal itself could elicit desire to drink, but there was no interaction effect when combined with cue exposure, that is, the combined effect on desire to drink was additive, not multiplicative (Cooney, Litt, Morse, Bauer, & Gaupp, 1997). Stasiewicz, Gulliver, Bradizza, Rohsenow, Torris, and Monti (1997) recommended caution in using emotional arousal cues; they found that exposure to negative emotional cues was associated with a *greater* urge to drink and with negative emotional responses. In view of the potential for a negative outcome, they recommended systematic study of exposure to emotional cues to identify the optimal duration that minimizes negative reactions.

Another factor that may impact responsivity to alcohol cues is clients' perception of actually being able to drink the alcohol used as a cue. Laberg (1990) demonstrated that the most successful way to elicit cravings in the laboratory was to inform participants that they would be allowed to consume the alcohol that was shown to them in the cue-exposure paradigm.

Beyond the basic question regarding reactivity to alcohol cues, another issue is whether cue reactivity predicts future drinking. In the Cooney et al. (1997) study, the desire to drink that was aroused by cue exposure plus emotional arousal did predict time to relapse. Rohsenow et al. (1994) found that salivation in response to cue exposure predicted drinking frequency after 3 months, but the urge to drink in the cue-exposure situation was not predictive. Hence, there is some evidence for a relationship between cue-elicited responses and subsequent drinking, but lack of agreement as to which elicited responses are the best predictors and which outcome measures are the most sensitive indicators.

A recent meta-analysis of 41 cue-reactivity studies indicated that self-reported craving can be elicited by cue exposure but that physiological indexes (heart rate, sweat-gland activity, and skin temperature) are less influenced by cues, suggesting a possible dissociation between self-report and physiological measures (Carter & Tiffany, 1999). Alcoholics had a significantly smaller craving effect size (+0.53) than other addict groups (+1.18 to +1.29). Carter and Tiffany recommended further study of factors that may modulate cue reactivity, such as the personal salience of the eliciting stimuli, perceived availability of alcohol or drugs in the laboratory, and exploration of additional dependent variables.

The sound theoretical basis of the respondent conditioning model and the results of the meta-analysis indicate potential value in continuing research on cue reactivity, as do findings that, in some instances, cue reactivity can predict outcome (Cooney et al., 1997; Rohsenow et al., 1994). Nevertheless, the cue-exposure procedure has not been consistent, either in eliciting cue reactivity or in predicting subsequent drinking. Furthermore, the observation of Drummond et al. (1990) more than a decade ago, that no published human study has yet

demonstrated that cue-elicited responding is a causal factor in relapse, remains true at this time.

With respect to treatment interventions incorporating cue-exposure methodology, there are few controlled studies that assess drinking outcomes. Drummond and Glautier (1994) found that cue exposure was more effective than relaxation training, not in preventing relapse but in reducing drinking after the initial lapse and prolonging the time to heavy drinking. Monti et al. (1993b) found that cue exposure, with the addition of coping skills training during cue presentations, resulted in gains that were similar to standard treatment in the first 3 months posttreatment, but in the next 3 months, the cue-exposure group maintained its gains, whereas the comparison group worsened. Monti et al. attributed the superiority of the cue-exposure group to the concomitant coping skills training, not to the effects of cue extinction, a conclusion that was supported by a subsequent, larger study using similar interventions (Rohsenow et al., 2001). Thus, studies have shown that cue-exposure treatment, with or without concomitant coping skills training, reduced the severity of drinking but did not prevent the initial occurrence of drinking. In a study focused on training moderate drinking, Sitharthan, Sitharthan, Hough, and Kavanagh (1997) compared the use of cue exposure (with priming doses of alcohol) to cognitive-behavioral intervention. They found that cue exposure was superior at a 6-month follow-up in self-reported drinking frequency and quantity. They speculated that the priming dose of alcohol may have enhanced generalization of the effects of cue exposure to participants' natural environments. However, in another moderation-oriented cue-exposure treatment study that also employed priming doses of alcohol, Heather et al. (2000) found that a cue-exposure intervention was not superior to behavioral self-control training on various measures of outcome, regardless of clients' level of alcohol dependence. Nevertheless, when taken together, the findings of these various studies suggest possible benefits of cue exposure as a treatment procedure.

A potential limitation on the clinical usefulness of cue exposure is the difficulty of extinguishing certain conditioned responses, which may in part account for the treatment resistance of addictive behavior (Lynch, Fertziger, Teitelbaum, Cullen, & Gantt, 1973). Not only is cue extinction problematic, but there are also related problems that complicate the clinical application of the respondent conditioning model. These include (1) spontaneous recovery (the tendency for conditioned responses that were once extinguished to reappear later when their eliciting stimuli reoccur), (2) generalization (the extent to which stimuli somewhat different from those previously extinguished are able to elicit drinking), and (3) rapid reinstatement of conditioned responses after a priming dose of alcohol (Drummond et al., 1990). It was partly in response to the difficulty of extinguishing conditioned responses that efforts were made to enhance the cue-exposure procedure by teaching skills to cope with the effects of the conditioned stimuli (Drummond et al., 1990; Niaura et al., 1988).

In an effort to identify more potent cues for drinking, Litt, Cooney, and Morse (2000) examined drinking antecedents that occur in the natural environment, on

the assumption that some of the critical variables that elicit drinking may not have been captured in the laboratory. They compared cue-elicited cravings in the laboratory with cravings that occur in participants' natural environments, as reported on handheld computers. Cravings elicited in the laboratory via cue exposure were not predictive of subsequent drinking, but cravings recorded in the field were predictive of future drinking: they tended to grow prior to drinking and decline afterwards. These findings provide evidence for the possible benefit of field studies employing experience-sampling methodology as a means of identifying and studying factors that control drinking behavior.

As a final consideration in this section, a few studies have used cue-exposure methodology in medication trials of anticraving agents. Monti et al. (1999) found that naltrexone treatment resulted in a 24% reduction in patients' urges to drink in response to combined alcohol and mood cues, indicating a possible application of cue-exposure methodology in trials of antidrinking medications. However, the effect was limited: for some who continued to experience cue-induced urges, even though they were on naltrexone, there was no reduction in the magnitude of their urges. Robbins, Ehrman, Childress, and O'Brien (1992) also used a cue-reactivity procedure to investigate an anticraving medication for cocaine dependence. Although the medication was not effective, the investigators believed that the procedure was useful.

1.2. Research Opportunities

Cue-exposure research has been a bit embarrassing for conditioning theory due to the lack of reliable cue reactivity or a consistent relationship to drinking behavior. Perhaps the variables controlling reactivity are more varied and complex in their application to human behavior than had been anticipated from the laboratory studies on which our knowledge of conditioning phenomena is based. It may be necessary to revisit those basic phenomena, which were largely developed in animal models, to more thoroughly test their applicability to *in vivo* human behavior.

Nevertheless, the results of some of the cue-exposure treatment studies and the recent meta-analysis are promising enough that further studies seem warranted. These should include investigation of factors that may mediate or moderate cue reactivity, such as the perception of alcohol availability in cue-exposure situations, the use of priming doses of alcohol, and personal salience of the eliciting stimuli. In addition, exploration of a greater range of dependent variables may also be useful. Finally, there is need for further development of cue exposure combined with the training of coping responses that would enable clients to reduce the impact of the cues and for determination of which coping responses would be most appropriate to train for which types of cues. Such training should also seek to develop behaviors that would persist beyond the conclusion of the intervention, thereby prolonging the effect of the cue-exposure treatment.

Recent studies in participants' natural environment using handheld computers appear promising. Although they do not strictly employ cue-exposure methodology, the finding that cravings recorded in the field were associated with subsequent drinking, if replicated, may strengthen cue-exposure methodology by providing a means of identifying antecedents in the natural environment that are likely to precipitate relapse. Furthermore, the observation of a relationship between cravings reported in the field and negative affect (Litt et al., 2000) indicates the additional potential for identifying other *in vivo* factors, such as mood states, that may influence cue reactivity.

2. Contingency Management

The cue-exposure model focuses on antecedent stimuli that may act through some form of respondent conditioning to initiate drinking. In contrast, the contingency management model is based on operant conditioning theory and is more concerned with the events that follow behavior. From the latter perspective, substance use is a form of operant behavior that is maintained by the reinforcing effects of the substance itself and by social reinforcement. The treatment of excessive drinking involves eliminating or weakening naturally occurring reinforcements for drinking and providing reinforcement for abstinence by means of tangible reinforcers, such as vouchers for goods or services (Higgins & Petry, 1999). There was a spate of research on this approach in the alcoholism literature of the 1970s (Liebson, Tommasello, & Bigelow, 1978; Miller, 1975; Miller, Hersen, Eisler, & Watt, 1974). Subsequently, however, interest in using this approach centered primarily on drug dependence, and contingency management for alcoholism fell into disuse until very recently. When applied to drug problems, the contingency management approach has been more efficacious than comparison treatments for reducing substance use and retaining clients in treatment (Griffith, Rowan-Szal, Roark, & Simpson, 2000; Higgins & Silverman, 1999).

In addition to reinforcing drug abstinence, contingency management procedures have also been used to reinforce clinic attendance (Ersner-Hershfield, Connors, & Maisto, 1981) and compliance with naltrexone among opioid-dependent clients (Preston, Silverman, Umbricht, DeJesus, Montoya, & Schuster, 1999). Iguchi, Belding, Morral, Lamb, and Husband (1997) demonstrated that providing reinforcement for completing individually tailored therapeutic tasks resulted in better attendance and a significant improvement in abstinence rates, which were maintained even after explicit reinforcement was discontinued. The finding of sustained maintenance suggests the possibility that Iguchi's strategy brought participants into contact with naturally occurring reinforcers in their environments that maintained behavioral changes after removing the experimental contingencies. Recently, Petry, Tedford, and Martin (2001) described practical considerations that are likely to be helpful in applying contingency management to reinforce a wide range of positive behaviors in addition to reductions in substance use.

In a recent study with alcohol-dependent outpatients, Petry, Martin, Cooney, and Kranzler (2000) demonstrated that contingency management added to standard treatment improved both attendance and time to relapse. The use of other drugs was also reduced, even though drug use was not specifically targeted by the contingency management intervention. Reinforcement was contingent upon negative breathalyzer readings and upon clients' completion of steps related to their treatment goals, with bonuses for continuing compliance. Reinforcers were provided according to a variable ratio schedule: if clients met the criteria for reinforcement, they drew a coupon from a bowl; of the 250 coupons in the bowl, 25% had no value, 68% were worth \$1 of goods or services, 7% were worth \$20, and 1 coupon was worth \$100. This variable ratio procedure was effective, less expensive to implement than the more usual voucher system, and acceptable to clients. In another application of periodic reinforcement, Kirby, Marlowe, Festinger, Lamb, and Platt (1998) found enhanced cocaine abstinence and improved treatment retention with a reinforcement procedure that was gradually faded to a fixed-ratio six schedule (one voucher reinforcement for six consecutive cocaine-free urine specimens).

2.1. Gaps in Knowledge

A difficulty in implementing contingency management with alcoholics relates to the problem of verifying abstinence. Whereas urinalysis can usually detect illicit drug use during the preceding 2–3 days, neither serum, urine, nor breath analyses can detect alcohol use that occurred more than about 12 hours previously. Hence, the problem of reliably detecting drinking is a fundamental difficulty in applying contingency management to alcoholism. An additional concern is the propensity to relapse once the explicit reinforcement contingencies have been discontinued (e.g., Higgins, Budney, Bickel, Foerg, Ogden, & Badger, 1995). In this regard, the work of Iguchi et al. (1997) and Petry et al. (2001) offers a promising approach for transitioning from contrived reinforcers (vouchers) by strengthening behaviors that are likely to be reinforced naturally in the "real world."

2.2. Research Opportunities

Although much of the work in this area has focused on drug dependence, the feasibility of the contingency management approach with alcoholics has been amply demonstrated. The recent successes of variable- and fixed-ratio procedures should go a long way toward allaying concerns about cost and acceptability to clients. Expenses could be even further reduced if goods and services were donated by local merchants.

Although the Kirby et al. (1998) and Petry et al. (2000) studies demonstrated that schedules of periodic reinforcement can be both effective and practical, further work is required to determine optimal schedules for reinforcing abstinence and behaviors that support abstinence. Investigation of schedules should also include strategies for making reinforcements less frequent toward

the end of treatment, as in Kirby et al. (1998), and developing procedures for transferring from the use of voucher reinforcement early in treatment to reinforcements that occur naturally in the environment. The work of Iguchi et al. (1997) and Petry et al. (2001) on reinforcing behaviors that support sobriety provides a useful starting point for such efforts.

Another issue relates to methods for verifying that the behaviors targeted for reinforcement truly occurred, before reinforcing them. Since outpatient treatment sessions are usually held weekly, it would be useful to be able to verify abstinence for a major portion of the preceding week. Furthermore, additional procedures for verifying the occurrence of desired behaviors other than abstinence would also be useful. Given the promise of the findings thus far from contingency management studies, it would be worthwhile to pursue these various issues.

3. Coping Skills Training

Adopting a focus somewhat different from the behavioral approaches, cognitive-behavioral theory views alcohol dependence as a maladaptive way of coping with problems or meeting needs. From this viewpoint, as in operant theory, alcoholic drinking develops as a result of experiencing the reinforcing effects of alcohol, but this approach also takes into account cognitive and emotional antecedents and consequences of drinking and expectancies regarding the effects of alcohol (Monti, Abrams, Kadden, & Cooney, 1989). Coping skills deficits are considered a major risk factor for drinking, which is likely to continue in the absence of adequate skills for coping with the events that trigger and follow its use (Miller & Hester, 1989). Therefore, treatment focuses on developing skills to respond to the environmental, cognitive, and emotional antecedents and consequences of drinking (Miller & Mastria, 1977). This training also takes into account factors that may inhibit the use of coping skills and the importance of providing adequate practice of skills, so that they will be readily available for use whenever needed.

3.1. Gaps in Knowledge

Among the various therapies covered in this review, coping skills training has been the most widely studied. Three meta-analyses have ranked it either first (Holder et al., 1991) or second (Miller et al., 1995; Finney & Monahan, 1996) among alcoholism treatments on the basis of evidence for effectiveness. Nevertheless, when compared directly to other treatment approaches in trials using random assignment, coping skills training often fares no better in terms of main effects (e.g., Kadden, Cooney, Getter, & Litt, 1989; Project MATCH Research Group, 1997).

In a review of the efficacy of Cognitive Behavioral Treatment (CBT), Morgenstern and Longabaugh (2000) noted that, despite its strong theoretical

foundation and impressive efficacy data, no evidence fully supports its hypothesized mechanism of action. They expressed concern that inadequate understanding of the mechanism may impair the ability to replicate treatment successes and hinder efforts to enhance effectiveness. They identified four requirements that must be met to verify that acquisition of coping skills is the mechanism of CBT's effectiveness: (1) CBT must reduce symptoms more than a comparison treatment, (2) it must have a greater effect on coping skills, (3) drinking outcomes must covary with changes in clients' coping skills, and (4) inclusion of coping skills as a covariate in statistical analyses must reduce the impact of treatment on outcome. Morgenstern and Longabaugh found that the majority of studies failed to show either that coping behaviors were changed by CBT or covaried with treatment outcome. Among the few studies that provide at least some evidence for mediation, either CBT increased the use of coping behaviors more than a comparison treatment, but the change in coping was unrelated to outcome (or the study failed to examine that relationship), or changes in coping behavior were related to outcome but were not associated with the skills-based treatment.

Longabaugh and Morgenstern (1999) conducted a meta-analysis (actually a box-score analysis) focused exclusively on studies of the CBT skills-training approach. In this more focused analysis, they found that when CBT was applied as a stand-alone treatment or as aftercare, it was not superior to alternative treatments (but it did increase treatment effectiveness when added to another treatment). The stronger the alternative treatment to which CBT was compared, the less likely that CBT would be found more effective: it was superior to no-treatment control conditions and to treatments judged ineffective but was no more effective than robust treatments. Thus, CBT demonstrated efficacy but was not superior to alternative treatments, and little support was found for the hypothesis that it operates by enhancing coping skills. Although inconsistent with prior meta-analyses, these findings warrant serious consideration because of their focus on CBT and the attention paid to presumed mechanisms of action.

Based on these findings, Longabaugh and Morgenstern (1999) recommended that functional analyses be conducted to guide the selection of targets for behavioral change, that mastery criteria be specified as a standard against which to verify the adequacy of skills training, and that hypotheses about mediating variables be subjected to complete analyses. In addition, they suggested nesting CBT components within a "broad spectrum" clinical approach that includes other interventions such as motivational enhancement, community reinforcement, and behavioral marital therapy. However, none of those interventions has been evaluated by the criteria that Longabaugh and Morgenstern applied to CBT, so it cannot be assumed that they would necessarily enhance CBT's effectiveness.

Finally, a number of different schemes for categorizing coping strategies have been proposed and tested, such as active versus avoidant (e.g. Moser & Annis, 1996), cognitive versus behavioral (e.g., Chung, Langenbucher, Labouvie, Pandina, & Moos, 2001), and alcohol-specific versus general coping (e.g., Jones &

Lanyon, 1981; Moggi, Ouimette, Moos, & Finney, 1999; Wells, Catalano, Plotnick, Hawkins, & Brattesani, 1989). Findings have not been consistent across studies, and their interpretation is complicated by the different variants and combinations of the schemes that have been used in the various studies.

3.2. Research Opportunities

Many of the interventions used in CBT are based on scientifically derived learning principles. However, Morgenstern and Longabaugh (2000) have called to our attention that when those principles are applied to human problems, their scientific origins do not automatically confer the status of "scientifically verified." More thorough analysis is required to understand whether coping skills treatment truly deserves its high rankings in the meta-analyses. In particular, it will be necessary to analyze all critical elements of hypothesized mediational chains. This analysis, regardless of its outcome, is likely to provide valuable information and serve as a basis for improving coping skills interventions.

Further work will also be necessary to determine the relative effectiveness of CBT's various skills-training components, optimal combinations of them for different types of clients, and the optimal number and duration of treatment sessions (Monti, Rohsenow, Colby, & Abrams, 1995). Since compliance with homework is notoriously poor, development of compliance-enhancement methods may help to improve the treatment outcome picture described above. Further research is also needed to determine how much actual practice of skills is required, as opposed to simply identifying high-risk situations and being made aware of ways to cope with them. Finally, as Longabaugh and Morgenstern (1999) recommend, future studies of coping skills training should employ both functional analyses to tailor interventions for each participant and mastery criteria to assure the adequacy of the training provided.

With regard to determining which particular coping strategies are most effective, studies employing different schemes for characterizing coping strategies have produced divergent and sometimes conflicting results. Nevertheless, the pattern of results seems to indicate that certain overall strategies may be more effective than others. Further work is needed to systematically determine which strategies or combinations of them are most strongly related to treatment outcome and whether a general taxonomy for characterizing coping strategies can be derived.

4. Relapse Prevention

Relapse prevention (RP) is an inclusive approach that combines a number of treatment elements, with a heavy reliance on the training of coping skills to deal with situations that clients identify as high risk for relapse. Some studies characterized as RP were included within the skills-training category in the meta-analyses cited above.

4.1. Gaps in Knowledge

A review focused specifically on RP treatment studies (Carroll, 1996) found that RP demonstrated efficacy when compared to no treatment, was superior to attention or discussion control conditions about half the time, and was comparable to, but no better than, robust alternate treatments, similar to the findings of Longabaugh and Morgenstern (1999) for CBT studies in general. Carroll also found that RP is effective for sustaining the effects of treatment and reducing the severity of relapse episodes, but the benefits diminish at increasing intervals after treatment (see also Allsop, Saunders, Phillips, & Carr, 1997). A meta-analysis of RP studies (Irvin, Bowers, Dunn, & Wang, 1999) found that RP treatment had a greater impact on psychosocial functioning than on substance use and accounted for only a small proportion of variance in substance use outcomes. Both reviews of the RP literature recommend further work to determine whether particular RP components can be identified that provide most of the benefit.

A multisite trial to evaluate Marlatt's relapse taxonomy (Marlatt & Gordon, 1985), which serves as the basis for identifying individual clients' high-risk situations, found that interrater reliabilities and predictive validity were unsatisfactory (Longabaugh, Rubin, Stout, Zywiak, & Lowman, 1996; Maisto, Connors, & Zywiak, 1996; Stout, Longabaugh, & Rubin, 1996). In contrast, a multidimensional approach to classifying relapse episodes had greater predictive power (Zywiak, Connors, Maisto, & Westerberg, 1996). Among Marlatt's categories of risk, negative emotions were identified as a major relapse precipitant and had the best interrater agreement (Longabaugh et al., 1996), although it could not be determined whether negative emotions were the cause of relapse or were simply indicators of a maladaptive lifestyle (Connors, Longabaugh, & Miller, 1996). Either way, given the consistency of this finding across a number of studies, it was recommended that treatment programs screen clients for negative emotions (e.g., anxiety and affective disorders). Furthermore, based on a finding that the level of coping skills predicted treatment outcome (Miller, Westerberg, Harris, & Tonigan, 1996; Connors, Maisto, & Zywiak, 1996), it was also recommended that skills training for coping with negative emotions be provided (Connors, Longabaugh, & Miller, 1996).

Longabaugh et al. (1996) suggested that coding of relapse antecedents could be improved by adding client traits, personality factors, social/interpersonal factors, environmental factors, and more past events (not just the most recent one). They also made suggestions for enhancing the structure of the assessment interview, modifying the relapse categories, allowing the use of more than one category, and eliminating hierarchical classification rules.

4.2. Research Opportunities

A number of suggested improvements that emerged from the recent multisite evaluation of RP ought to be tested. The primary recommendation is that a broader schema for classifying of relapse episodes should be developed to include

client trait and personality factors, interpersonal and environmental factors, and multiple past events. Additional improvements that might also be tested include allowing the use of more than one relapse category for a trigger event and providing greater structure to the assessment interview to improve its reliability.

RP is a broad concept that has incorporated a variety of interventions under its umbrella. Research is needed to determine which components are the most effective and for whom, using decision criteria like those advocated by Longabaugh and Morgenstern (1999) for evaluating CBT.

Taken together, the findings that RP had a greater impact on psychosocial functioning than on drinking and that client coping skills were a strong predictor of outcome suggest that coping skills training is an important element of RP strategy. Further development of coping skills training may thus help to enhance the maintenance of treatment gains for longer periods of time.

5. Behavioral Marital Therapy

The inclusion of a client's spouse/partner in treatment increases the likelihood of identifying relationship problems that may trigger or reinforce substance use and provides a means of educating the partner how best to support the client's recovery efforts (McCrady & Epstein, 1996). The behavioral approach to alcoholism treatment with couples seeks to identify relationship conflicts that trigger drinking, improve communications in strained relationships, and develop reinforcing consequences for abstinence (Epstein & McCrady, 1998). Behavioral marital therapy, it has been shown, is associated with reduced domestic violence (O'Farrell, Van Hutton, & Murphy, 1999), reduced verbal aggression (O'Farrell, Murphy, Neavins, & Van Hutton, 2000), improvements in marital functioning, reduced treatment attrition, and reduced alcohol consumption, although relapse to alcohol use is common (McCrady, Epstein, & Hirsch, 1999; McKay, Longabaugh, Beattie, Maisto, & Noel, 1993). Longabaugh, Wirtz, Beattie, and Noel (1995) found that adding just a small amount of relationship enhancement to CBT was helpful for those who had nonproblematic relationships but that a more extended intervention was necessary for those with problematic relationships. Fals-Stewart, O'Farrell, and Birchler (1997) found that behavioral couples therapy was both more effective and more cost-effective than individual therapy for reducing substance use, sustaining abstinence, and reducing legal, family, and social problems.

5.1. *Gaps in Knowledge*

In a review of various marital and family therapy approaches, O'Farrell (1995) found that behavioral treatment focusing on both substance use and relationship issues was effective and superior to individually focused treatment. Nevertheless, he noted that behavioral marital therapy has not become popular, despite its empirical support, and is "used infrequently, if at all" (p. 217). To bridge the gap between research and clinical practice, he recommended replicating promising

findings and extending them to broader populations, including minorities, families in which the wife is the identified patient, and cases with comorbid psychopathology. He also recommended investigating the impact of marital therapy on the children in the family and exploring means of promoting long-term recovery.

McCrary and Epstein (1996) note that one possible obstacle to broader use of this treatment approach is the complexity of treating individuals each of whom may have their own psychopathology and whose interactions with each other may be disorganized and destructive.

Given reports of deteriorating benefits over time, especially among more severe cases, O'Farrell, Choquette, and Cutter (1998) added 15 RP sessions during the year following behavioral marital therapy. The RP sessions had an initial positive impact on both drinking and marital outcomes, but the improvements in drinking were not sustained as long as those in marital adjustment. The RP component had a more durable effect if the alcohol and marital problems were more severe at the outset. In contrast, McCrary et al. (1999) found that adding RP to behavioral marital therapy resulted in a *shorter* interval from the end of treatment until the onset of heavy drinking, although the duration of drinking episodes was briefer.

5.2. Research Opportunities

A number of questions about behavioral marital therapy remain unanswered. Some involve basic issues such as the optimal duration and intensity of treatment, active ingredients, and mediators of change and their relationship to outcome (Epstein & McCrary, 1998). Additional work is needed to extend the duration of positive effects, improve outcomes for those with severe problems, and adapt the approach for use in the presence of psychiatric disorders and for couples in which both partners are alcohol- or drug-dependent (Epstein & McCrary, 1998). Other areas for investigation include the impact of varying degrees of relationship distress, level of commitment to the relationship, presence of domestic violence, impact on children, applicability to minorities, and applicability to families in which the wife is the identified patient. It may also be fruitful to investigate whether certain patient or family characteristics may be indicators of family systems that are appropriate for these interventions.

Given the potential benefits of the marital therapy approach, some attention should also be paid to its underutilization to identify factors that deter its use and to find means of increasing its use in both clinical and research settings. Finally, the issue of concurrent RP treatment requires clarification to ascertain conditions under which it is likely to be helpful and those in which it is not.

6. Final Note

The total number of recommendations in the sections above may seem like a very ambitious research agenda. However, there are various areas of redundancy due to overlap among the interventions: (1) Coping skills training and

RP (as well as CRA, covered elsewhere in this volume) all include comparable (sometimes identical) components. Findings regarding the effectiveness of those components would apply to all interventions that employ them, as would findings that specify which of the components are most effective for clients with particular characteristics or needs. (2) The call for studies focused on prolonging the effects of treatment was repeated several times; any developments in this area are likely to have broad applicability. (3) Some combinations of approaches (e.g., contingency management combined with CRA; Budney & Higgins, 1998) have already been tested, and other combinations might be devised in future studies, thereby reducing the number of separate treatment categories. (4) Finally, additional basic research, aimed at a better understanding of the way learning principles identified in the laboratory apply to *in vivo* human behavior, would also have broad applicability.

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References

- Allsop, S., Saunders, B., Phillips, M., & Carr, A. (1997). A trial of relapse prevention with severely dependent male problem drinkers. *Addiction* 92, 61–74.
- Budney, A.J., & Higgins, S.T. (1998). *A Community Reinforcement Plus Vouchers Approach: Treating Cocaine Addiction*. Rockville, MD: National Institute on Drug Abuse.
- Carroll, K.M. (1996). Relapse prevention as a psychosocial treatment: A review of controlled clinical trials. *Experimental and Clinical Psychopharmacology* 4, 46–54.
- Carter, B.L., & Tiffany, S.T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction* 94, 327–340.
- Chung, T., Langenbucher, J., Labouvie, E., Pandina, R.J., & Moos, R.H. (2001). Changes in alcoholic patients' coping responses predict 12-month treatment outcomes. *Journal of Consulting and Clinical Psychology* 69, 92–100.
- Connors, G.J., Longabaugh, R., & Miller, W.R. (1996). Looking forward and back to relapse: Implications for research and practice. In C. Lowman, J. Allen, & W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S191–S196.
- Connors, G.J., Maisto, S.A., & Zywiak, W.H. (1996). Understanding relapse in the broader context of post-treatment functioning. In C. Lowman, J. Allen, and W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S173–S189.
- Cooney, N.L., Litt, M.D., Morse, P.A., Bauer, L.O., & Gaupp, L. (1997). Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. *Journal of Abnormal Psychology* 106, 243–250.
- Drummond, D.C., Cooper, T., & Glautier, S.P. (1990). Conditioned learning in alcohol dependence: Implications for cue exposure treatment. *British Journal of Addiction* 85, 725–743.
- Drummond, D.C., & Glautier, S. (1994). A controlled trial of cue exposure treatment in alcohol dependence. *Journal of Consulting and Clinical Psychology* 62, 809–817.
- Epstein, E.E., & McCrady, B.S. (1998). Behavioral couples treatment of alcohol and drug use disorders: Current status and innovations. *Clinical Psychology Review* 18, 689–711.

- Ersner-Hershfield, S.M., Connors, G.J., & Maisto, S.A. (1981). Clinical and experimental utility of refundable deposits. *Behaviour Research and Therapy* 19, 455–457.
- Fals-Stewart, W., O'Farrell, T.J., & Birchler, G.R. (1997). Behavioral couples therapy for male substance-abusing patients: A cost outcomes analysis. *Journal of Consulting and Clinical Psychology* 65(5), 789–802.
- Finney, J.W., & Monahan, S.C. (1996). The cost-effectiveness of treatment for alcoholism: A second approximation. *Journal of Studies on Alcohol* 29, 229–243.
- Griffith, J.D., Rowan-Szal, G.A., Roark, R.R., & Simpson, D.D. (2000). Contingency management in outpatient methadone treatment: A meta-analysis. *Drug and Alcohol Dependence* 58, 55–66.
- Heather, N., Brodie, J., Wale, S., Wilkinson, G., Luce, A., Webb, E., & McCarthy, S. (2000). A randomized controlled trial of moderation-oriented cue exposure. *Journal of Studies on Alcohol* 61, 561–570.
- Higgins, S.T., Budney, A.J., Bickel, W.K., Foerg, F.E., Ogden, D., & Badger, G.J. (1995). Outpatient behavioral treatment for cocaine dependence: One-year outcome. *Experimental and Clinical Psychopharmacology* 3, 205–212.
- Higgins, S.T., & Petry, N.M. (1999). Contingency management: Incentives for sobriety. *Alcohol Research and Health* 23, 122–127.
- Higgins, S.T., & Silverman, K. (1999). *Motivating Illicit-Drug Abusers to Change Their Behavior: Research on Contingency Management Interventions*. Washington, DC: APA Books.
- Holder, H., Longabaugh, R., Miller, W.R., & Rubonis, A.V. (1991). The cost effectiveness of treatment for alcoholism: A first approximation. *Journal of Studies on Alcohol* 52, 517–540.
- Iguchi, M.Y., Belding, M.A., Morral, A.R., Lamb, R.J., & Husband, S.D. (1997). Reinforcing operants other than abstinence in drug abuse treatment: An effective alternative for reducing drug use. *Journal of Consulting and Clinical Psychology* 65, 421–428.
- Irvin, J.E., Bowers, C.A., Dunn, M.E., & Wang, M.C. (1999). Efficacy of relapse prevention: A meta-analytic review. *Journal of Consulting and Clinical Psychology* 67, 563–570.
- Jones, S.L., & Lanyon, R.I. (1981). Relationship between adaptive skills and outcome of alcoholism treatment. *Journal of Studies on Alcohol* 42, 521–525.
- Kadden, R.M., Cooney, N.L., Getter, H., & Litt, M.D. (1989). Matching alcoholics to coping skills or interactional therapies: Posttreatment results. *Journal of Consulting and Clinical Psychology* 57, 698–704.
- Kazdin, A.E. (1982). History of behavior modification. In A.S. Bellack, M. Hersen, & A.E. Kazdin (eds.), *International Handbook of Behavior Modification and Therapy*. New York: Plenum Press, pp. 3–32.
- Kirby, K.C., Marlowe, D.B., Festinger, D.S., Lamb, R.J., & Platt, J.J. (1998). Schedule of voucher delivery influences initiation of cocaine abstinence. *Journal of Consulting and Clinical Psychology* 66, 761–767.
- Laberg, J.C. (1990). What is presented, and what prevented, in cue exposure and response prevention with alcohol dependent subjects? *Addictive Behaviors* 15, 367–386.
- Liebson, I., Tommasello, A., & Bigelow, G. (1978). A behavioral treatment of alcoholic methadone patients. *Annals of Internal Medicine* 89, 342–344.
- Litt, M.D., Cooney, N.L., Kadden, R.M., & Gaupp, L. (1990). Reactivity to alcohol cues and induced moods in alcoholics. *Addictive Behaviors* 15, 137–146.
- Litt, M.D., Cooney, N.L., & Morse, P. (2000). Reactivity to alcohol-related stimuli in the laboratory and in the field: Predictors of craving in treated alcoholics. *Addiction* 95, 889–900.
- Longabaugh, R., & Morgenstern, J. (1999). Cognitive-behavioral coping-skills therapy for alcohol dependence: Current status and future directions. *Alcohol Research and Health* 23, 78–85.
- Longabaugh, R., Rubin, A., Stout, R.L., Zywiak, W.H., & Lowman, C. (1996). The reliability of Marlatt's taxonomy for classifying relapses. In C. Lowman, J. Allen, & W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S73–S88.
- Longabaugh, R., Wirtz, P.W., Beattie, M.C., & Noel, N. (1995). Matching treatment focus to patient social investment and support: 18-month follow-up results. *Journal of Consulting and Clinical Psychology* 63, 296–307.

- Lynch, J.J., Fertziger, A.P., Teitelbaum, H.A., Cullen, J.W., & Gantt, W.H. (1973). Pavlovian conditioning of drug reactions: Some implications for problems of drug addiction. *Conditional Reflex* 8, 211–223.
- Maisto, S.A., Connors, G.J., & Zywiak, W.H. (1996). Construct validation analyses on the Marlatt typology of relapse precipitants. In C. Lowman, J. Allen, and W.R. Miller (eds.). *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S89–S97.
- Marlatt, G.A., & Gordon, J.R. (eds.) (1985). *Relapse Prevention*. New York: Guilford.
- McCrady, B.S., & Epstein, E.E. (1996). Theoretical bases of family approaches to substance abuse treatment. In F. Rotgers, D.S. Keller, & J. Morgenstern (eds.), *Treating Substance Abuse. Theory and Technique*. New York: Guilford, pp. 117–142.
- McCrady, B.S., Epstein, E.E., & Hirsch, L.S. (1999). Maintaining change after conjoint behavioral alcohol treatment for men: Outcomes at 6 months. *Addiction* 94(9), 1381–1396.
- McKay, J.R., Longabaugh, R., Beattie, M.C., Maisto, S.A., & Noel, N.E. (1993). Does adding conjoint therapy to individually focused alcoholism treatment lead to better family functioning? *Journal of Substance Abuse* 5, 45–59.
- Miller, P. (1975). A behavioral intervention program for public drunkenness offenders. *Archives of General Psychiatry* 32, 915–918.
- Miller, P.M., Hersen, M., Eisler, R.M., & Watt, J.G. (1974). Contingent reinforcement of lowered blood/alcohol levels in an outpatient chronic alcoholic. *Behavior Research and Therapy* 12, 261–263.
- Miller, P.M., & Mastria, M.A. (1977). *Alternatives to Alcohol Abuse: A Social Learning Model*. Champaign, IL: Research Press.
- Miller, W.R., Brown, J.M., Simpson, T.L., Handmaker, N.S., Bien, T.H., Luckie, L.F., Montgomery, H.A., Hester, R.K., & Tonigan, J.S. (1995). What works? A methodological analysis of the alcohol treatment outcome literature. In R.K. Hester & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, 2nd ed. NJ: Allyn and Bacon, pp. 12–44.
- Miller, W.R., & Hester, R.K. (1989). Treating alcohol problems: Toward an informed eclecticism. In R.K. Hester and W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*. New York: Pergamon Press, pp. 3–13.
- Miller, W.R., Westerberg, V.S., Harris, R.J., & Tonigan, J.S. (1996). What predicts relapse? Prospective testing of antecedent models. In C. Lowman, J. Allen, & W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S155–S171.
- Moggi, F., Ouimette, P.C., Moos, R.H., & Finney, J.W. (1999). Dual diagnosis patients in substance abuse treatment: Relationship of general coping and substance-specific coping to 1-year outcomes. *Addiction* 94, 1805–1816.
- Monti, P.M., Abrams, D.B., Kadden, R.M., & Cooney, N.L. (1989). *Treating Alcohol Dependence: A Coping Skills Training Guide*. New York: Guilford.
- Monti, P.M., Rohsenow, D.J., Colby, S.M., & Abrams, D.B. (1995). Coping and social skills training. In R.K. Hester and W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, 2nd ed. NJ: Allyn and Bacon, pp. 221–241.
- Monti, P.M., Rohsenow, D.J., Hutchison, K.E., Swift, R.M., Mueller, T.I., Colby, S.M., Brown, R.A., Gulliver, S.B., Gordon, A., & Abrams, D.B. (1999). Naltrexone's effect on cue-elicited craving among alcoholics in treatment. *Alcoholism: Clinical and Experimental Research* 23, 1386–1394.
- Monti, P.M., Rohsenow, D.J., Rubonis, A.V., Niaura, R.S., Sirota, A.D., Colby, S.M., & Abrams, D.B. (1993a). Alcohol cue reactivity: Effects of detoxification and extended exposure. *Journal of Studies on Alcoholism* 54, 235–245.
- Monti, P.M., Rohsenow, D.J., Rubonis, A.V., Niaura, R.S., Sirota, A.D., Colby, S.M., Goddard, P., & Abrams, D.B. (1993b). Cue exposure with coping skills treatment for male alcoholics: A preliminary investigation. *Journal of Consulting and Clinical Psychology* 61, 1011–1019.
- Morgenstern, J., & Longabaugh, R. (2000). Cognitive-behavioral treatment for alcohol dependence: A review of evidence for its hypothesized mechanisms of action. *Addiction* 95, 1475–1490.
- Moser, A.E., & Annis, H.M. (1996). The role of coping in relapse crisis outcome: A prospective study of treated alcoholics. *Addiction* 91, 1101–1113.
- Niaura, R.S., Rohsenow, D.J., Binkoff, J.A., Monti, P.M., Pedraza, M., & Abrams, D.B. (1988). Relevance of cue reactivity to understanding alcohol and smoking relapse. *Journal of Abnormal Psychology* 97, 133–152.

- O'Farrell, T.J. (1995). Marital and family therapy. In R.K. Hester and W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, 2nd ed. Boston: Allyn and Bacon, pp. 195–220.
- O'Farrell, T.J., Choquette, K.A., & Cutter, H.S.G. (1998). Couples relapse prevention sessions after behavioral marital therapy for male alcoholics: Outcomes during the three years after starting treatment. *Journal of Studies on Alcohol* 59, 357–370.
- O'Farrell, T.J., Murphy, C.M., Neavins, T.M., & Van Hutton, V. (2000). Verbal aggression among male alcoholic patients and their wives in the year before and two years after alcoholism treatment. *Journal of Family Violence* 15, 295–310.
- O'Farrell, T.J., Van Hutton, V., & Murphy, C.M. (1999). Domestic violence before and after alcoholism treatment: A two-year longitudinal study. *Journal of Studies on Alcohol* 60, 317–321.
- Perry, N.M., Martin, B., Cooney, J.L., & Kranzler, H.R. (2000). Give them prizes and they will come: Contingency management for treatment of alcohol dependence. *Journal of Consulting and Clinical Psychology* 68, 250–257.
- Perry, N.M., Tedford, J., & Martin, B. (2001). Reinforcing compliance with non-drug-related activities. *Journal of Substance Abuse Treatment* 20, 33–44.
- Pomerleau, O.F., Fertig, J., Baker, L., & Cooney, N. (1983). Reactivity to alcohol cues in alcoholics and non-alcoholics: Implications for a stimulus control analysis of drinking. *Addictive Behaviors* 8(1), 1–10.
- Preston, K.L., Silverman, K., Umbricht, A., DeJesus, A., Montoya, I.D., & Schuster, C.R. (1999). Improvement in naltrexone treatment compliance with contingency management. *Drug and Alcohol Dependence* 54, 127–135.
- Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–29.
- Robbins, S.J., Ehrman, R.N., Childress, A.R., & O'Brien, C.P. (1992). Using cue reactivity to screen medications for cocaine abuse: A test of amantadine hydrochloride. *Addictive Behaviors* 17, 491–499.
- Rohsenow, D.J., Monti, P.M., Abrams, D.B., Rubonis, A.V., Niaura, R.S., Sirota, A.D., & Colby, S.M. (1992). Cue elicited urge to drink and salivation in alcoholics: relationship to individual differences. *Advances in Behaviour Research and Therapy* 14, 195–210.
- Rohsenow, D.J., Monti, P.M., Rubonis, A.V., Gulliver, S.B., Colby, S.M., Binkoff, J.A., & Abrams, D.B. (2001). Cue exposure with coping skills training and communication skills training for alcohol dependence: 6- and 12-month outcomes. *Addiction* 96, 1161–1174.
- Rohsenow, D.J., Monti, P.M., Rubonis, A.V., Sirota, A.D., Niaura, R.S., Colby, S.M., Wunschel, S.M., & Abrams, D.B. (1994). Cue reactivity as a predictor of drinking among male alcoholics. *Journal of Consulting and Clinical Psychology* 62, 620–626.
- Rohsenow, D.J., Niaura, R.S., Childress, A.R., Abrams, D.B., & Monti, P.M. (1991). Cue reactivity in addictive behaviors: Theoretical and treatment implications. *The International Journal of the Addictions* 25, 957–990.
- Rotgers, F. (1996). Behavioral theory of substance abuse treatment: Bringing science to bear on practice. In F. Rotgers, D.S. Keller, & J. Morgenstern (eds.), *Treating Substance Abuse. Theory and Technique*. New York: Guilford, pp. 174–201.
- Rubonis, A., Colby, S.M., Monti, P.M., Rohsenow, D.J., Gulliver, S.B., & Sirota, A.D. (1994). Alcohol cue reactivity and mood induction in male and female alcoholics. *Journal of Studies on Alcohol* 55, 487–494.
- Sitharthan, T., Sitharthan, G., Hough, M.J., & Kavanagh, D.J. (1997). Cue exposure in moderation drinking: A comparison with cognitive-behavior therapy. *Journal of Consulting and Clinical Psychology* 65, 878–882.
- Stasiewicz, P.R., Gulliver, S.B., Bradizza, C.M., Rohsenow, D.J., Torris, R., & Monti, P.M. (1997). Exposure to negative emotional cues and alcohol cue reactivity with alcoholics: A preliminary investigation. *Behaviour Research and Therapy* 35, 1143–1149.
- Stout, R.L., Longabaugh, R., & Rubin, A. (1996). Predictive validity of Marlatt's relapse taxonomy versus a more general relapse code. In C. Lowman, J. Allen, & W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S99–S110.

Wells, E.A., Catalano, R.F., Plotnick, R., & Hawkins, J.D. (1989). General versus drug-specific coping skills and posttreatment drug use among adults. *Psychology of Addictive Behaviors* 3, 8–21.

Zywiak, W.H., Connors, G.J., Maisto, S.A., & Westerberg, V.S. (1996). Relapse research and the reasons for drinking questionnaire: A factor analysis of Marlatt's relapse taxonomy. In C. Lowman, J. Allen, and W.R. Miller (eds.), *Perspectives on Precipitants of Relapse*. Supplement to *Addiction* 91, S121–S130.

The Community Reinforcement Approach

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Abstract. This chapter reviews two behavioral substance abuse treatments: The Community Reinforcement Approach (CRA) and Community Reinforcement and Family Training (CRAFT). Both of these programs were built on the concept that an individual's recovery is greatly affected by his or her unique environment. This environment, or reinforcing "community," is composed of family, friends, work/school, social activities, and perhaps spiritual affiliations. CRA, the first of these two programs to be developed, was created specifically for the problem drinker (Hunt & Azrin, 1973). The goal of CRA is to rearrange multiple aspects of an individual's "community" so that a clean and sober lifestyle is more rewarding than one that is dominated by alcohol and drugs. Subsequently, CRAFT was developed for the many individuals with substance abuse problems who are vehemently opposed to treatment (Institute of Medicine, 1990). CRAFT works through concerned family members and friends of these treatment refusals in an effort to get them to seek therapy (Sisson & Azrin, 1986). Descriptions and the empirical support for CRA and CRAFT follow.

1. Community Reinforcement Approach (CRA)

1.1. *CRA Description*

CRA is a comprehensive behavioral intervention for treating substance abuse problems. Developed in accordance with the belief that environmental contingencies play a crucial role in an individual's use and recovery, CRA utilizes familial, social, recreational, and occupational reinforcers to support individuals in changing their drinking behaviors. The goal is to construct an environment that rewards sobriety and discourages substance use (Azrin, 1976; Hunt & Azrin, 1973).

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The CRA program begins with a functional analysis of the drinking behavior. This semistructured interview identifies the internal and external triggers for typical drinking episodes, as well as the positive and negative consequences associated with alcohol use. Once the drinking triggers are outlined, the therapist can either assist in developing a plan to avoid these high-risk situations or teach the necessary skills for addressing them. The positive consequences that maintain drinking are examined so that healthy substitutes can be found. The negative consequences reported by the drinkers represent things of value they feel they have lost and therefore might be willing to work to regain. Next, the program introduces "sobriety sampling," a negotiation process between client and therapist to establish a period of sobriety. This motivational technique helps clients "buy in" to their treatment plan, since it makes them an integral part of the decision-making process. This is in contrast to many traditional methods that tell clients from day one that they *cannot* and *must not* ever drink again. Such a goal tends to be intimidating and unrealistic for many clients and consequently either frightens them away or sets them up for failure. Regardless of the length of the negotiated period of sobriety within the CRA program, some clients require disulfiram (Antabuse) to abet this. In these circumstances, it is essential to have a supportive disulfiram monitor (Azrin, Sisson, Meyers, & Godley, 1982; Meyers & Smith, 1995). This trusted relative or friend administers the disulfiram while using positive communication and contacts the therapist if the client refuses to take the disulfiram several days in a row.

As part of CRA treatment, the client's happiness in other areas of life not directly related to drinking is examined as well. The CRA Happiness Scale provides a precounseling baseline of satisfaction across 10 problem areas, and subsequent administrations of the scale are used to monitor progress. Behavioral goals and strategies are regularly established and updated. Enhancing happiness in other life areas often requires skills training (e.g., problem solving, communication skills), and so this is introduced as needed. Further, if clients report employment or relationship dissatisfaction, behavioral counseling in these areas is provided. Importantly, CRA also focuses on clients' social and recreational lives. As clients reduce their drinking, they often have difficulty replacing that behavior with enjoyable, healthy activities or social circles not centered around alcohol. Because the early stages of recovery are sometimes precarious, methods for preventing and addressing relapse are an integral part of the CRA program (Meyers & Smith, 1995; Smith & Meyers, 2001; Smith, Meyers, & Miller, 2001).

The CRA intervention is appropriate for a wide range of clients, including both those with final goals to reduce drinking and those with aspirations to abstain. CRA is effective in inpatient and outpatient settings and with alcohol problems ranging from mild to severe (Azrin, 1976; Azrin et al., 1982; Smith, Meyers, & Delaney, 1998). Although the earliest studies were conducted exclusively in rural settings, more recent trials took place in urban areas with ethnically diverse populations (Miller, Meyers, Tonigan, & Grant, 2001; Smith et al., 1998).

CRA is a "package" that is tailored to meet the client's specific needs. The program contains a number of procedures that can be used or omitted, depending on the client's skills and goals. For example, an unemployed client may find the Job Club component of value. The behavioral skills training elements of the CRA package (e.g., drink refusal) are used for clients with specific skill deficits. CRA relationship therapy is an option for clients with significant others. Hence, CRA has the flexibility to be applied to individual clients with differing needs, and this flexibility also allows combining it with self-help groups.

1.2. CRA Empirical Support

1.2.1 CRA Reviews. CRA has been repeatedly ranked among the top programs in reviews of treatments for alcoholism conducted during the last decade, regardless of the manner in which treatment efficacy was defined and measured (Holder, Longabaugh, Miller, & Rubonis, 1991; Miller et al., 1995). Most impressive was CRA's number one position in a cost-effectiveness analysis by Finney and Monahan (1996). A recent review of controlled alcohol treatment programs by Miller and Wilbourne (2002) ranked the various interventions by taking into account the studies' methodological quality and the strength of the support for treatment efficacy. CRA again was ranked near the top of the list; its score placed it fourth out of 50 treatment modalities.

1.2.2. CRA Inpatient Trials. Azrin and colleagues conducted the first CRA studies in the early 1970s. In both experiments, they compared CRA to a standard 12-step alcohol treatment program used in a state hospital. The latter entailed traditional Alcoholics Anonymous objectives and strategies, which were based on the work of Jellinek's disease model (Jellinek, 1960). Their findings provided evidence for CRA's superior effectiveness. In the original matched control study by Hunt and Azrin (1973), the eight participants in the CRA condition did significantly better on several outcome variables than the eight standard treatment group participants. For example, individuals in the CRA group spent significantly less time drinking and institutionalized and more time employed and with their families. At the 6-month follow-up, the CRA group reported drinking on 14% of the follow-up days, whereas the control group reported drinking on 79% of those days. Azrin's (1976) second CRA trial with inpatients revealed similar positive findings. There were several changes in the CRA program in this later study, including a disulfiram (Antabuse) compliance program that involved a supportive monitor, increased social support through the use of a buddy system, and an early warning (relapse) notification system. The results showed that the CRA group made greater progress toward recovery than the standard 12-step treatment group. For example, at the 6-month follow-up, the CRA group reported drinking alcohol only 2% of the time, compared to 55% of the time for the control group. Furthermore, CRA participants had a significantly higher rate of employment, spent more time with family, and less time institutionalized. More importantly,

these results persisted through the 2-year follow-up; the CRA group remained abstinent 90% of the time.

1.2.3. CRA Outpatient Trials. The third CRA study investigated its effectiveness with 43 outpatients (Azrin et al., 1982). One particular interest was in testing the contribution of the disulfiram compliance program (with its supportive monitor), compared simply to giving disulfiram prescriptions. Clients were randomly assigned to one of three conditions. The traditional group received 12-step counseling and a disulfiram prescription. The Antabuse Assurance group received 12-step counseling, a disulfiram prescription, and disulfiram compliance training. The CRA Plus Antabuse Assurance group received the CRA procedures outlined in the previous study (including disulfiram compliance training) and several new procedures: sobriety sampling, motivational counseling, and drink refusal. The two groups that received the disulfiram compliance training had the highest abstinence rates overall. At the 6-month follow-up, the abstinence rates for the CRA Plus Antabuse Assurance, Antabuse Assurance, and traditional treatment were 97%, 74%, and 45%, respectively. A surprising finding was that married participants in the Antabuse Assurance group had significantly better drinking outcomes than single individuals. In fact, their drinking success equaled that of participants in the CRA Plus Antabuse Assurance condition on several variables. In employment, the most pronounced 6-month differences were between the traditional group's unemployed days (36% of the month) and the CRA Plus Antabuse Assurance's (7% of the month).

More recently, Miller and colleagues (Miller, Meyers, Tonigan, & Grant, 2001) replicated and extended the original CRA outpatient study with a much larger sample ($n = 237$). The typical clients in this study were males (83%) approximately 30 years of age. On average, participants had completed high school, but the majority were only working part-time (16%) or not at all (41%). As for marital status, 46% were single and 22% were married; the remaining 32% was divorced, separated, or widowed. Ethnic representation was primarily Hispanic (56%) and Anglo (38%).

The design retained the 1982 study's conditions of traditional treatment, traditional treatment plus disulfiram compliance (i.e., Antabuse Assurance), and CRA plus disulfiram compliance. But three new conditions were added to tease out the effects of disulfiram. The first new condition was CRA without disulfiram, which was created to ascertain whether disulfiram was an essential component of the CRA program. These four conditions just noted were for disulfiram-eligible participants. The remaining two new conditions were CRA and traditional treatment for disulfiram-ineligible participants—drinkers who either were unwilling or medically unable to take disulfiram as part of the treatment. These conditions were included primarily to determine whether being ineligible to take disulfiram (for medical or perhaps motivational reasons) would affect treatment outcome differentially.

For the disulfiram-eligible participants, those who received the CRA program had significantly better drinking outcomes than the traditional treatment

condition at the proximal follow-ups (months 1–6). The most pronounced difference was between the percentage of drinking days for the CRA participants (3%) and those in the traditional treatment (without disulfiram, 19%). However, there was no significant difference between the CRA condition and the traditional treatment that included disulfiram-compliance training. At the distal follow-ups (months 12 and 18), the significant group differences that previously favored CRA were also lost. Interestingly, although there were no significant differences in drinking outcome for the new disulfiram-ineligible conditions, the drop-out rate for CRA (9%) was significantly lower than that for traditional treatment (41%).

In examining the question of why there were not more reliable differences that favored CRA over traditional treatment in this one study, one might first note that individuals in the traditional treatment which included disulfiram-compliance training actually received an important component of CRA. Compliance training entails involving family members in treatment and teaching them positive communication skills. Given the empirical support for behavioral couples therapy in the alcohol field (O'Farrell & Fals-Stewart, 2000), the added success with this behavioral couples component probably should not be surprising. It was also the case that a much higher percentage of individuals in the traditional group with compliance training took disulfiram (90%) than those in the comparable CRA group (56%). Furthermore, therapists for the traditional group *without* a compliance training program still readily encouraged its participants to take disulfiram, and more than half of them did so. So in essence, much of the success of the traditional group may have been due to the disulfiram, albeit this cannot be used to explain the equivalence of the disulfiram-ineligible conditions. Regardless, the reason behind the traditional group's greater acceptance of disulfiram and use of monitors merits further study.

It is also possible that the overlap between treatment conditions may not have been limited to the planned disulfiram-compliance training. The therapists for the traditional group with disulfiram compliance were CRA counselors by training. Although they were supposedly delivering only 12-step based therapy, it is conceivable that old habits die hard. And given that sessions were not audio- or videotaped in this earlier trial (Miller et al., 2001), treatment integrity could not be checked thoroughly. Still, the results should be viewed in perspective, given that overall there was a 75% reduction in drinking quantity and frequency from baseline to the distal follow-up points.

1.2.4. Examination of Individual Components of CRA. The purpose of the Social Club component of CRA is to provide an opportunity for clients to practice their new social skills in a nonthreatening, alcohol-free atmosphere and to offer an enjoyable activity to compete with drinking during high-risk times. Mallams, Godley, Hall, and Meyers (1982) studied the effects of CRA's Social Club by dividing 34 participants into two conditions, Encouragement and Minimum Awareness. The Encouragement group received verbal support from

their counselors to attend the Social Club and were provided with transportation if desired. The Minimum Awareness group was simply informed about the Social Club and was provided with directions for finding it. The results showed that the Encouragement group frequented the Social Club more often than the Minimum Awareness group. The Encouragement group also drank significantly less alcohol; their intake averaged 0.8 ounces per day compared to the Minimum Awareness's average daily intake of 3.3 ounces.

The disulfiram-compliance training component of the CRA package was examined separately in two randomized trials interested in both cocaine and alcohol use (Carroll et al., 1993; Carroll, Nich, Ball, McCance, & Rounsville, 1998). The results showed that cocaine-dependent individuals who received disulfiram-compliance training as part of their treatment protocol had significantly more cocaine and alcohol abstinence than individuals who did not receive it. In all probability, the excessive drinking was serving as a trigger for cocaine use. When the alcohol was targeted through monitored disulfiram, the cocaine use dropped as well.

1.2.5. CRA with Homeless Individuals. Recently, CRA's effectiveness with homeless alcohol-dependent individuals was studied by Smith and colleagues in Albuquerque (Smith et al., 1998; Smith & Delaney, 2001). A total of 106 eligible homeless individuals (86% male) completed the intake assessment. On average, they were 38 years old and had graduated from high school. The ethnic breakdown was 64% White, 19% Hispanic, 13% Native American, and 4% African-American. Forty-six percent were never married, and 91% were unemployed. Participants were randomly assigned to either the CRA group or the homeless shelter's standard treatment. The latter consisted of free access to 12-step substance abuse counselors, on-site AA meetings, case managers for the dually diagnosed, a temporary job placement program, and standard shelter services (e.g., free meals, clothing, showers, mail distribution, telephones). The CRA program was modified to better suit a homeless population. This included using a group therapy format and providing specialized skills groups (e.g., independent living) in addition to the usual ones. The Social Club activity was decided weekly by the CRA participants and often was a leisurely Friday night dinner hosted by therapists at a restaurant. A subset of eligible CRA participants was assigned to take disulfiram as part of its program. Given the shortage of significant others to serve as their disulfiram monitors, the disulfiram was administered in a group by the project nurse. Participants in both conditions were provided grant-funded housing under the stipulation of abstinence during this 3–4 month program. Breathalyzer tests were conducted periodically, and offenders were temporarily suspended from housing.

Program involvement was generally good; CRA participants attended an average of 39 groups and five individual sessions. The one exception was the Job Club training, where the average number of sessions attended was only three. As expected, the main treatment components used for the standard condition were AA meetings and the day shelter's temporary job placement service.

Although precise numbers were unavailable regarding job service participation, the average number of AA meetings attended during the first 2-months of the program was 19. Overall involvement in the follow-up assessments was noteworthy as well for this transient population; follow-up rates ranged from a low of 76% at 12 months to a high of 93% at 2 months.

Results showed that drinking was reduced substantially for both conditions, with average daily consumption dropping from 19 drinks to 3.8 drinks. However, the CRA participants' drinking outcomes (quantity and frequency) were significantly better than those of the standard condition, with this difference being most pronounced through the 9-month follow-up. A secondary interest was in examining the contribution of disulfiram as part of the CRA program. Contrary to expectations, eligible individuals who were randomly assigned to supplement their CRA treatment with monitored disulfiram showed no advantage in outcomes. Both the CRA and standard groups showed dramatic improvements in housing status. The rates of homelessness averaged less than 20% across the five follow-ups. The one significant housing difference occurred at the 4-month follow-up; the CRA group had more participants housed. Regarding employment status, though there were noteworthy pre-to-post improvements, there were no group differences. Specifically, at intake, only 9% were employed, and at 12-months, 55% was employed. However, many of these individuals were working part-time; they worked an average of 11 days out of the last 30 days. Future CRA research with homeless individuals should concentrate on adding elements that target employment outcomes and address the special needs of women (e.g., victimization).

1.2.6. CRA with Adolescents. The most recent use of CRA was with an adolescent sample. The 114 participants were 12–17 years old (76% male) who had stayed in a residential treatment center for at least 7 days. Of the sample, 74% were Caucasian, and 17% were African-American. One-third of the sample had not completed more than the eighth grade in school, 90% were unemployed, and 82% had prior involvement with the juvenile justice system. All participants met the criteria for a DSM-IV substance use disorder; with 57% alcohol-dependent and 90% marijuana-dependent.

Participants were randomly assigned to one of two types of aftercare groups. The Usual Continuing Care (UCC) condition was a referral to local outpatient providers for continuing care after residential discharge. These programs ranged from meeting 1–5 days a week and offered a variety of services: self-help groups, urine testing and feedback, relapse prevention, skills training, and counseling for parents as well as the adolescent. The second condition was the Community Reinforcement Approach (Meyers & Smith, 1995) adapted for adolescents (ACRA; Godley et al., 2001). The ACRA group participants attended significantly more treatment sessions (92%) than the UCC group (59%). At the 3-month follow-up, the ACRA group members had reduced their days of alcohol use significantly more than those assigned to the UCC group and were significantly more abstinent from marijuana than the UCC group as well

(M. Godley, S. Godley, Dennis, Funk, Rodney, & Passetti, 2002). Additional follow-up data are still being collected.

1.2.7. CRA with Illicit Drug Users. Although originally created as a treatment for alcohol problems, some researchers have extended CRA's application to illicit drugs. When treating cocaine dependence, CRA typically is combined with a contingency management program that rewards clean urine samples with vouchers that can be exchanged for material goods. Financial reinforcers are used to supplement the CRA program for individuals with cocaine problems to address their high early attrition rates and to compete with the strong reinforcing effects of cocaine at the onset of treatment. Higgins and colleagues have been primarily responsible for demonstrating the efficacy of the CRA plus voucher program for cocaine-addicted individuals (e.g., Higgins et al., 1993, 1995). Recent studies attempted to tease apart the contribution of contingent vouchers from that of the CRA program. The findings were somewhat mixed, depending on the outcome measure selected and the length of the follow-up period examined (see Higgins et al., 1994; Higgins, Wong, Badger, Haug Ogden, & Dantona, 2000).

The utility of CRA as part of a treatment protocol for opiate-addicted individuals has been tested as well. Bickel and colleagues compared a CRA plus voucher condition with standard drug counseling for individuals undergoing buprenorphine detoxification (Bickel, Amass, Higgins, Badger, & Esch, 1997). Half of the vouchers could be earned for opiate-free urines, and half could be awarded for engaging in treatment-prescribed activities. Participants in the CRA plus voucher condition were significantly more likely to complete the detoxification program and to achieve longer documented periods of opioid abstinence than those in standard treatment. CRA *without* the voucher component was used to treat methadone-maintained individuals in another study (Abbott, Weller, Delaney, & Moore, 1998). The researchers found that significantly more participants assigned to the CRA condition achieved a minimum of 3 weeks of continuous abstinence and showed greater improvement on the Addiction Severity Index drug composite score than the standard counseling condition.

2. Community Reinforcement and Family Training (CRAFT)

2.1. *CRAFT Description*

CRAFT grew out of the CRA program when it became apparent that family members could play an important role in engaging a resistant loved one in alcohol treatment. In part, this discovery came from substance abusers themselves (the identified patients; IPs), who often reported that their decision to seek treatment was prompted by a concerned significant other (CSO; Cunningham, Sobell, Sobell, & Kapur, 1995). Given the extensive contact between CSOs and IPs and the CSOs' direct access to powerful IP reinforcers

and contingencies, it appeared reasonable to teach CSOs behavioral procedures for positively influencing the IP's behavior. So CRAFT was developed with three main objectives: to ultimately encourage treatment-refusing drinkers to enter therapy, to get the IPs to decrease their use in the meantime, and to enhance the CSOs' satisfaction with their own lives regardless of their IP's outcome.

The specific CRAFT components overlap a fair degree with the CRA program's procedures. CRAFT components include (1) a functional analysis of the IP's drinking episodes as reported by the CSO; to outline the IP's typical drinking triggers and consequences so that options become apparent for altering the CSO's own behavior toward the IP during the earliest signs of upcoming use or in response to the drinking; (2) the assessment of danger and domestic violence; to determine whether it is safe to have the CSO try new ways of interacting with the IP and to prevent violence; (3) contingency management training; to teach CSOs that they can influence the rates of specific IP behavior by manipulating the consequences that follow it; (4) communication training; to eliminate reciprocal blaming and defensiveness so that CSOs will have better success in positively influencing their loved one's using behavior and eventually engaging them in treatment; (5) the planning of IP activities to compete with drinking; to increase the chance that the IP will select healthy behaviors over drinking; (6) an emphasis on improving the quality of the CSO's own life; to focus on the need for CSOs to reinforce themselves positively; (7) preparation of the CSO to invite the IP to sample treatment; to prepare the CSO to suggest treatment in the most positive and supportive manner and at an opportune time; and (8) discussion of the importance of supporting the IP once in treatment; to increase the likelihood that the IP remains in treatment and succeeds (Meyers, Miller, & Smith, 2001; Meyers & Smith, 1997).

Interestingly, CRAFT is nearly a photographic negative of the more common Al-Anon approach that encourages CSOs to accept their powerlessness to influence the drinker, to detach, and to concentrate on taking care of their own needs. CRAFT, in contrast, empowers and encourages CSOs to systematically reinforce "the right stuff." It is also different from the Johnson Institute intervention, even though both programs seek treatment engagement for the IP. The latter program's confrontational style is at odds with CRAFT's emphasis on positive reinforcement.

2.2. *CRAFT Empirical Support*

2.2.1. CRAFT Alcohol Trials. Sisson and Azrin (1986) conducted the first study examining the viability of using community-based reinforcement procedures with a problem drinker's CSO. They randomly assigned 12 CSOs to receive either an early version of CRAFT (Community Reinforcement Training: CRT) or a disease model/Al-Anon approach. The latter condition entailed weekly individual counseling sessions, as well as encouragement to attend Al-Anon meetings. The results were that six of seven resistant drinkers with CSOs in

the CRT condition entered treatment after an average of 58.2 days and 7.2 CSO sessions. In contrast, none of the traditional group's drinkers sought treatment. Furthermore, the drinkers associated with CRT already had reduced their drinking frequency by more than half by the time they started the program. Specifically, CSOs reported during their own intake that the IPs were drinking approximately 24 days that month. This decreased to 11 days per month while the CSOs alone were in treatment. The drinking pattern of the IPs in the disease model condition remained virtually unchanged.

In a recent large trial funded by the National Institute on Alcohol Abuse and Alcoholism, 130 CSOs were randomized into one of three different engagement approaches: (1) Al-Anon facilitation therapy, which was designed to encourage involvement in the 12-step program and to get resistant drinkers to enter formal treatment; (2) the Johnson Institute intervention, which prepared the CSO for a confrontational family meeting that led to formal treatment; and (3) CRAFT, which taught behavioral change skills and new strategies for guiding the drinker into treatment. All three therapies were manual-based and consisted of 12 hours of planned contact. CSO participants were primarily female (91%) and were comprised of spouses (59%); parents (30%); and romantic partners, children, or grandparents (11%) of the IPs. In terms of ethnicity, CSOs were mainly White, non-Hispanic (53%), and Hispanic (39%) individuals. CSOs averaged 47 years of age and 14 years of education. The majority were employed either full-time (51%) or part-time (17%). They were recruited primarily for the study via a newspaper ad that offered free treatment to the loved ones of treatment-refusing problem drinkers.

IPs were considered "engaged" in treatment if they completed the 4-hour assessment battery and scheduled a therapy session within 6 months of the CSO's intake. Results demonstrated that CRAFT was significantly more effective in engaging resistant drinkers in treatment (64%), compared with the Al-Anon (13%) and Johnson Institute (30%) interventions (Miller, Meyers, & Tonigan, 1999). Regarding attendance, CSOs in the Al-Anon group participated in a slightly higher number of the 12 scheduled sessions (95%) than the CSOs in the CRAFT group (89%), whereas CSOs assigned to the Johnson Institute intervention attended only 53% of their sessions. Still, the high attendance rates for the Al-Anon group *did not* serve as an advantage in terms of engagement. If one specifically examines the length of time required by the CRAFT-trained CSOs to get their resistant drinkers into treatment, the median number of days was 47, with an average of only 4.7 CSO sessions required. Importantly, the median number of sessions attended by IPs who began treatment was 10.5.

Although no between-group differences were found in CSOs' functioning, there were marked improvements from pre- to posttreatment on all five CSO dependent measures. These were in the areas of depression (Beck Depression Inventory; Beck, Steer, & Garbin, 1988), anger (State-Trait Anger Expression Inventory; Spielberger, Jacobs, Russell, & Crane, 1983), family cohesion and conflict (Family Environment Scale; Moos & Moos, 1986), and general happiness (Happiness Scale; Azrin, Naster, & Jones, 1973). These CSO findings were

independent of whether or not their IP ever entered treatment. This methodologically sound study had a large and diverse sample, and steps were taken to ensure that potential IPs were initially treatment-*refusing* individuals with serious alcohol problems. Additionally, experienced therapists followed manual-guided therapy approaches, and follow-up rates were high (e.g., 94% at 12 months).

2.2.2. CRAFT Illicit Drug Trials. The success of the CRAFT program is not limited to treatment-refusing drinkers, but extends to illicit drug users as well. In an uncontrolled pilot study, an engagement rate of 74% was obtained for 62 CRAFT-trained CSOs (Meyers, Miller, Hill, & Tonigan, 1999). A controlled trial in Philadelphia detected significantly higher engagement rates (64%) for CRT (i.e., CRAFT) than for a 12-step intervention (17%; Kirby, Marlowe, Festinger, Garvey, & LaMonca, 1999). In a second randomized clinical trial, 90 CSOs of illicit drug users were assigned to one of three treatments: (a) CRAFT, (b) CRAFT plus additional group sessions after the completion of the individual sessions (CRAFT + aftercare), or (c) Al-Anon/Nar-Anon Facilitation Therapy (Al-Nar FT) in an individual format (Meyers, Miller, Smith & Tonigan, 2002). Most of the CSOs were female (88%), and half were of Hispanic origin (49%). In each condition, the majority of the CSOs were either parents or romantic partners of the treatment-resistant IP.

Overall, a significant relationship was found between CSO group assignment and IP engagement status. The successful engagement rates were CRAFT (58.6%), CRAFT plus aftercare (76.7%), and Al-Nar FT (29.0%). Although the CRAFT plus aftercare group had the highest engagement rate, this difference was not significantly better than the CRAFT-alone group. Both the combined and individual CRAFT groups successfully engaged resistant IPs significantly more often than the Al-Nar FT group. Once engaged, IPs attended an average of 7.6 therapy sessions.

3. Summary

Both CRA and CRAFT are empirically sound, cost-effective alcohol treatment programs that have wide applicability. CRA has proven efficacious for demographically diverse populations with a range of problems and needs. More recently, CRAFT studies have shown that it is a more successful program than the commonly used approaches for engaging unmotivated substance abusers. Furthermore, CRAFT engagement is possible not only through spouses, but through other family members and friends as well. Together, these findings clearly demonstrated that these community reinforcement approaches merit careful consideration when selecting alcohol treatment programs.

References

- Abbott, P.J., Weller, S.B., Delaney, H.D., & Moore, B.A. (1998). Community Reinforcement Approach in the treatment of opiate addicts. *American Journal of Drug and Alcohol Abuse* 24, 17-30.

- Azrin, N. (1976). Improvements in the community-reinforcement approach to alcoholism. *Behaviour Research and Therapy* 14, 339–348.
- Azrin, N., Naster, B.J., & Jones, R. (1973). Reciprocity counseling: A rapid learning-based procedure for marital counseling. *Behaviour Research and Therapy* 11, 365–382.
- Azrin, N., Sisson, R.W., Meyers, R.J., & Godley, M. (1982). Alcoholism treatment by disulfiram and community reinforcement therapy. *Journal of Behavior Therapy and Experimental Psychiatry* 13, 105–112.
- Beck, A.T., Steer, R.A., & Garbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review* 8, 77–100.
- Bickel, W.K., Amass, L., Higgins, S.T., Badger, G.J., & Esch, R. A. (1997). Effects of adding behavioral treatment to opioid detoxification with buprenorphine. *Journal of Consulting and Clinical Psychology*, 65, 803–810.
- Carroll, K.M., Ziedonis, D., O'Malley, S., McCance-Katz, E., Gordon, L., & Rounsaville, B. (1993). Pharmacologic interventions for alcohol- and cocaine-abusing individuals: A pilot study of disulfiram vs. naltrexone. *The American Journal on Addictions* 2, 77–79.
- Carroll, K.M., Nich C., Ball, S.A., McCance, E., & Rounsaville, B.J. (1998). Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 93, 713–728.
- Cunningham, J.A., Sobell, L.C., Sobell, M.B., & Kapur, G. (1995). Resolution from alcohol treatment problems with and without treatment: Reasons for change. *Journal of Substance Abuse* 7, 275–372.
- Finney, J.W., & Monahan, S.C. (1996). The cost-effectiveness of treatment for alcoholism: A second approximation. *Journal of Studies on Alcohol* 57, 229–243.
- Godley, S.H., Meyers, R.J., Smith, J.E., Godley, M.D., Titus, J.M., Karvinen, T., Dent, G., Passetti, L., & Kelberg, P. (2001). *The Adolescent Community Reinforcement Approach for Adolescent Cannabis Users, Cannabis Youth Treatment (CYT) Series*, Vol. 4. Rockville, MD: Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration.
- Godley, M.D., Godley, S.H., Dennis, M.L., Funk, Rodney, & Passetti, L.L. (2002). A randomized trial of an assertive continuing care protocol for adolescents discharged from residential treatment: Preliminary outcomes. *Journal of Substance Abuse Treatment* 23 21–32.
- Higgins, S.T., Budney, A.J., Bickel, W.K., Hughes, J.R., Foerg, F., & Badger, G. (1993). Achieving cocaine abstinence with a behavioral approach. *American Journal of Psychiatry* 150, 763–769.
- Higgins, S.T., Budney, A.J., Bickel, W.K., Foerg, F.E., Ogden, D., & Badger, G.J. (1995). Outpatient behavioral treatment for cocaine dependence: One-year outcome. *Experimental and Clinical Psychopharmacology* 3, 205–212.
- Higgins, ST., Budney, A.J., Bickel, Foerg, F., Donham, R. & Badger, G.J. (1994). Incentives improve treatment retention and cocaine abstinence in ambulatory cocaine-dependent patients. *Archives of General Psychiatry* 51, 568–576.
- Higgins, S.T., Wong, C.J., Badger, G.J., Haug Ogden, D.E., & Dantona, R.L. (2000). Contingent reinforcement increases cocaine abstinence during outpatient treatment and one year of follow-up. *Journal of Consulting and Clinical Psychology* 68, 64–72.
- Holder, H., Longabaugh, R., Miller, W.R., & Rubonis, A. (1991). The cost effectiveness of treatment for alcoholism: A first approximation. *Journal of Studies on Alcohol* 52, 517–540.
- Hunt, G.M., & Azrin, N.H. (1973). A community-reinforcement approach to alcoholism. *Behaviour Research and Therapy* 11, 91–104.
- Institute of Medicine. (1990). *Treating Drug Problems*, Vol. 1. Washington, DC: National Academy Press.
- Jellinek, E.M. (1960). *The Disease Concept of Alcoholism*. New Haven, CT: Hillhouse Press.
- Kirby, K.C., Marlowe, D.B., Festinger, D.S., Garvey, K.A., & LaMonca, V. (1999). Community reinforcement training for family and significant others of drug abusers: A unilateral intervention to increase treatment entry of drug users. *Drug and Alcohol Dependence* 56, 85–96.
- Mallams, J.H., Godley, M.D., Hall, G.M., & Meyers, R.J. (1982). A social-systems approach to resocializing alcoholics in the community. *Journal of Studies on Alcohol* 43, 1115–1123.
- Meyers, R.J., Miller, W.R., Hill, D.E., & Tonigan, J.S. (1999). Community reinforcement and family training (CRAFT): Engaging unmotivated drug users in treatment. *Journal of Substance Abuse* 10(3), 291–308.

- Meyers, R.J., Miller, W.R., & Smith J.E. (2001). Community reinforcement and family training (CRAFT). In R. Meyers & W. Miller (eds.), *A Community Reinforcement Approach to Addiction Treatment*. UK: University Press, pp. 147–160.
- Meyers, R.J., Miller, W.R., Smith, J.E., & Tonigan, J.S. (2002). A randomized trial of two methods for engaging treatment-refusing drug users through concerned significant others. *Journal of Consulting and Clinical Psychology*, 70, 1182–1185.
- Meyers, R.J., & Smith, J.E. (1995). *Clinical Guide to Alcohol Treatment: The Community Reinforcement Approach*. New York: Guilford.
- Meyers, R.J., & Smith, J.E. (1997). Getting off the fence: Procedures to engage treatment-resistant drinkers. *Journal of Substance Abuse Treatment* 14(5), 467–472.
- Miller, W.R., Brown, J.M., Simpson, T.L., Handmaker, N.S., Bein, T.H., Luckie, L.F., Montgomery, H.A., Hester, R.K., & Tonigan, J.S. (1995). What works? A methodological analysis of the alcohol treatment outcome literature. In R. Hester & W. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*. Needham Heights, MA: Allyn & Bacon.
- Miller, W.R., Meyers, R.J., & Tonigan J.S. (1999). Engaging the unmotivated in treatment for alcohol problems: A comparison of three intervention strategies. *Journal of Consulting and Clinical Psychology* 67, 688–697.
- Miller, W.R., Meyers, R.J., Tonigan J.S., & Grant, K.A. (2001). Community reinforcement and traditional approaches: Findings of a controlled trial. In R. Meyers & W. Miller (eds.), *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: University Press, pp. 79–103.
- Miller, W.R., & Wilbourne, P.L. (2002). Mesa Grande: A methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 97, 265–277.
- Moos, R.H., & Moos, B.S. (1986). *Family Environment Scale Manual*. Palo Alto CA: Consulting Psychologist Press.
- O'Farrell, T.J., & Fals-Stewart, W. (2000). Behavioral couples therapy for alcoholism and drug abuse. *Journal of Substance Abuse Treatment* 18, 51–54.
- Sisson, R.W., & Azrin, N.H. (1986). Family-member involvement to initiate and promote treatment of problem drinkers. *Journal of Behavior Therapy and Experimental Psychiatry* 17, 15–21.
- Smith, J.E., & Delaney, H.D. (2001). CRA with the homeless. In R. Meyers & W. Miller (eds.), *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: University Press, pp. 104–122.
- Smith, J.E., & Meyers, R.J. (2001). The treatment. In R. Meyers & W. Miller (eds.), *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: University Press, pp. 28–61.
- Smith, J.E., Meyers, R.J., & Delaney, H. (1998). The community reinforcement approach with homeless alcohol-dependent individuals. *Journal of Consulting and Clinical Psychology* 66, 541–548.
- Smith, J.E., Meyers, R.J., & Miller, W.R. (2001). The community reinforcement approach to the treatment of substance use disorders. *The American Journal of Addictions* 10 (suppl), 51–59.
- Spielberger, C.D., Jacobs, G., Russell, S., & Crane, R.S. (1983). Assessment of anger: The state-trait anger scale. In J.N. Butcher & C.D. Spielberger (eds.), *Advances in Personality Assessment*, Vol. 2. Hillsdale, NJ.: Erlbaum, pp. 159–187.

IV

Pharmacotherapy

Raye Z. Litten, Section Editor

Overview

Raye Z. Litten

During the past decade, significant advances have been made in discovering, developing, and clinically testing promising medications. At the end of the 1980s, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) was funding a half-dozen human pharmacotherapy trials. During the 1990s, more than 50 such trials were supported, and several have yielded intriguing and valuable findings. NIAAA, however, has not been alone in accelerating support for development of medications for alcoholism treatment. Important research on medications development has been conducted overseas, and the pharmaceutical industry has begun to commit itself to developing and testing medications to treat alcoholics. So far, naltrexone and acamprosate have been the two most demonstrably successful medications.

Naltrexone, an opioid antagonist, was approved by the Food and Drug Administration (FDA) in 1994, the first medication approved for alcoholism treatment in more than 50 years since the introduction of disulfiram. The efficacy studies on which the approval was based were two NIAAA-supported studies of Volpicelli, Alterman, Hayashida, and O'Brien (1992) and O'Malley, Jaffe, Chang, Schottenfeld, Meyer, and Rounsvaille (1992). Naltrexone represents a new generation of medications that act to directly reduce the urge or craving to drink. NIAAA is supporting a host of studies to better understand the clinical potential as well as the limitations of naltrexone. Many of these projects have been completed, and the results are under analysis. Several significant clinical questions are being addressed such as how long should patients receive naltrexone, what is the optimal dose, what types of alcoholics respond best to naltrexone, which behavioral therapy should be used in conjunction with naltrexone to optimize outcome, and last, can combining naltrexone with other medications further enhance outcome. In this section, Drs. O'Malley and

Froehlich will review the preclinical and clinical studies on the effects of naltrexone on maintenance of abstinence, relapse to heavy drinking, and patterns of drinking. In addition, the authors will discuss mechanisms of action, identify factors predicting clinical response to naltrexone, explore various dosing regimens, discuss the efficacy of naltrexone in nonalcoholic populations, and present recent findings on the combination of naltrexone with other medications.

Acamprosate (Campral) has been studied extensively in Europe in 16 separate trials, employing more than 4500 alcohol-dependent subjects. In nearly every study, acamprosate improved rates of abstinence and increased treatment retention during a treatment period of 3 months to 1 year. Lipharm Pharmaceuticals has recently completed a 21-site U.S. trial, the results of which are being submitted to the FDA as part of a New Drug Application for U.S. approval. Interestingly, acamprosate's site of action in the brain is quite different from that of naltrexone. It appears to interact with the glutamate system, although its precise mechanism is still unclear. NIAAA is supporting several investigations to better understand the mechanism of action of acamprosate and is also supporting a cooperative agreement for a multisite pharmacological and behavioral trial known as COMBINE. In this trial, acamprosate and naltrexone, both alone and in combination, are being studied in the context of two types of behavioral therapies. Dr. Mason will review the earlier European clinical trials of acamprosate, discuss its mechanism of action, and describe its safety profile.

In the 1980s, serotonergic agents were the most promising pharmacological agents for treating alcoholism. In particular, it has been shown that selective serotonin reuptake inhibitors (SSRIs) reduce alcohol intake by up to 60 to 80% in various animal models (Gorelick, 1989). However, human clinical trials of SSRIs produced, at best, mixed results. Studies yielded an array of efficacy rates ranging from no effect to a substantial effect in both nondepressed and depressed alcoholics. Drs. Pettinati, Kranzler, and Madaras will present an overview of serotonin-selective pharmacotherapy discussing the relationship between serotonergic activity and alcohol dependence, summarizing the trials of various serotonergic agents, and demonstrating how the effects of serotonergic agents may relate alcoholic subtypes.

To date, the medications available produce small to medium effects and may assist many, but not all, alcoholics. A high priority of NIAAA is to discover and evaluate new medications that are more potent in preventing or reducing drinking. Advances have been made in understanding the neuroscience of alcohol drinking behavior. Instead of one neurotransmitter system, many are involved including opioid, glutamate, GABA, serotonin, and dopamine systems as well as hormonal systems such as the hypothalamic-pituitary-adrenal axis, a system involved in responding to stress. These findings have led to many exciting opportunities for developing new drugs that modulate these systems. In addition, research is being conducted to identify the neural circuits involved in alcohol drinking, determine the genes underlying alcoholism, and explore intracellular signaling pathways (e.g., second messenger systems, protein kinases) that influence or regulate alcohol use, dependence, tolerance, and

withdrawal. Integration of this knowledge is expected to lead to new and even more effective medications. Dr. Koob will address many of these issues focusing primarily on the opioid system and present ways of testing new promising pharmacological agents using various animal models of alcohol consumption.

In summary, the chapters in this section present an excellent overview of medications development for alcoholism. The authors interestingly and articulately identify recent advances in medications development, describe the current state of the field, and provide important insights into future prospects for research.

References

- Gorelick, D.A. (1989). Serotonin uptake blockers and the treatment of alcoholism. In M. Galanter (ed.), *Recent Developments in Alcoholism*, Vol. 7. New York: Plenum Press (pp. 267–281).
- O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry* 49, 881–887.
- Volpicelli, J.R., Alterman, A.I., Haysashida, M., & O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49, 876–880.

Acamprosate

Barbara J. Mason

Acamprosate was approved for use in France in 1989, and more recently, in most European and South American countries, as well as in Australia, Hong Kong, and South Africa. To date, more than 1.5 million alcohol-dependent patients worldwide have been treated with the drug. A double-blind, placebo-controlled, multicenter, 6-month trial in 601 alcohol-dependent patients has recently been conducted in support of regulatory approval in the United States (for a review of the methodology of this study, see Mason and Ownby, 2000).

The goal of this chapter is to familiarize the U.S. alcoholism researcher and treatment provider with available data on the safety and efficacy of acamprosate for treating alcohol dependence. Reviewed below are the results of all published, double-blind, placebo-controlled clinical trials of acamprosate among alcohol-dependent outpatients. Methodology and quantitative outcome data for all studies are summarized in Table 1.

1. Overview of Clinical Trials

The published efficacy and safety studies of acamprosate treatment of alcohol dependence are comprised of 16 controlled clinical trials conducted in 11 European countries and involving more than 4500 alcohol-dependent outpatients. All of these studies have been published and are reviewed in detail below (Table 1 shows trial summaries). Clinical research methods tend to be consistent across trials and are summarized in the next section. Efficacy and safety results follow. Trials are grouped according to duration. Studies involving

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Table 1. Acamprose's Efficacy in Alcohol-Dependent Outpatients: A Summary of Randomized, Double-Blind, Placebo-Controlled Clinical Trials

Country (Reference)	N	% of Patients Abstinent at Day 1 ^a	Months of Study/ Follow-Up	Dose	Days to First Drink	Rate of Total Abstinence, % ^b	Cumulative Abstinence Duration ^c		Treatment Completion, %
							Cumulative Abstinence Duration	NR ^e	
Short-term efficacy studies									
France (Lhuillier et al., 1985)	85 (Acamprose: 42, placebo: 43)	100	3/0	25 g/kg/d	NR	Acamprose: 61 ^d , placebo: 32	NR ^d	NR ^d	Acamprose: 47, placebo: 37
France (Lhuillier et al., 1990)	569 (Acamprose: 279, placebo: 290)	100	3/3	1332 mg/d	NR ^a	Acamprose: 29, placebo: 33	NR ^a	NR ^a	Acamprose: 61, placebo: 62
Belgium (Rousseaux et al., 1996)	127 (Acamprose: 63, placebo: 64)	100	3/0	ABW ^a	NR ^a	Acamprose: 1998 mg: 51 ^d , 1998 mg: 56 ^d	NR ^a	NR ^a	Acamprose: 31, placebo: 29
Belgium/France (Pelc et al., 1997)	188 (Acamprose: 126, placebo: 62)	100	3/0	1332 mg/d (N = 63)	Acamprose, 1998 mg/d (N = 63)	Acamprose, 1332 mg: 56 ^d , placebo: 15	Acamprose, 1332 mg: 44 ^d , placebo: 26	Acamprose, 1332 mg: 59% ^d , placebo: 26	Acamprose, 1998 mg: 66 ^d , 1998 mg: 63% ^d , placebo: 52
Long-term efficacy studies									
Belgium (Pelc et al., 1992)	102 (Acamprose: 55, placebo: 47)	100	6/6	ABW ^a	NR ^a	Acamprose: 24 ^d , placebo: 4	NR ^a	NR ^a	Acamprose: 60 d ^d , placebo: 21
Switzerland (Ladewig et al., 1993)	61 (Acamprose: 29, placebo: 32)	100	6/6	ABW ^a	NR ^a	Acamprose: 38 ^d , placebo: 17	NR ^a	NR ^a	Acamprose: 43% ^d , placebo: 24%
Belgium, the Netherlands, and Luxembourg (Geerlings et al., 1997)	262 (Acamprose: 128, placebo: 134)	100	6/6	ABW ^a	Acamprose: 45 ^d , placebo: 15	Acamprose: 20 ^d , placebo: 10	Acamprose: 34% ^d , placebo: 24%	Acamprose: 41 ^d , placebo: 31	Acamprose: 72% ^d , placebo: 53% ^d , placebo: 38
Italy (Poldrugo, 1997)	246 (Acamprose: 122, placebo: 124)	100	6/6	ABW ^a	Acamprose: 151 ^d , placebo: 61	Acamprose: 43 ^d , placebo: 30	Acamprose: 59%, placebo: 30	Acamprose: 77 d, placebo: 81 d	Acamprose: 66% ^d , placebo: 54% ^d
United Kingdom (Chick et al., 2000)	581 (Acamprose: 289, placebo: 292)	68	6/15	1998 mg/d	Acamprose: 37, placebo: 40	Acamprose: 34, placebo: 39	Acamprose: 77 d, placebo: 81 d	Acamprose: 35, placebo: 35	Acamprose: 66% ^d , placebo: 54% ^d
Italy (Tempesta et al., 2000)	330 (Acamprose: 164, placebo: 166)	100	6/3	1998 mg/d	Acamprose: 158 ^d , placebo: 58	Acamprose: 58 ^d , placebo: 45	Acamprose: 45%, placebo: 45	Acamprose: 76% ^d , placebo: 74	Acamprose: 49% ^d , placebo: 36% ^d
Portugal (Barrius et al., 1997)	302 (Acamprose: 150, placebo: 152)	100	6/12	ABW ^a	Acamprose: 111 ^d , placebo: 55	Acamprose: 39 ^d , placebo: 26	Acamprose: 55%, placebo: 55	Acamprose: 57% ^d , placebo: 55	Acamprose: 49% ^d , placebo: 35% ^d
Spain (Gual and Lehert, 2001)	288 (Acamprose: 147, placebo: 141)	0	6/0	1998 mg/d	NR ^a	Acamprose: 35 ^d , placebo: 26	Acamprose: 93%, placebo: 74	Acamprose: 65, placebo: 61	Acamprose: 65, placebo: 61

Longer term efficacy studies						
Germany (Sass et al., 1996) ¹⁴	272 (Acamprose: 136, placebo: 136)	100	12/12	ABW ^a	Acamprose: 165 ^d , Placebo: 43 ^d	Acamprose: 62%, Placebo: 58%
Austria (Whitworth et al., 1996) ¹⁵	448 (Acamprose: 224, placebo: 224)	100	12/12	ABW ^a	Acamprose: 55 ^d , Placebo: 18 ^d	Acamprose: 139 d, Placebo: 104 d
Dose-ranging study						
France (Faillé et al., 1995) ²¹	538 (Acamprose: 361, placebo: 177)	100	12/6	1998 mg/d (N = 173) Acamprose, 1332 mg/d (N = 185) Acamprose, 1332 mg: 136 ^d , placebo: 102	Acamprose, 1998 mg: 153 ^d , Acamprose, 1332 mg: 18.1, placebo: 11.3	Acamprose, 1998 mg: 223 d ^d , Acamprose, 1332 mg: 198 d ^d , placebo: 173 d
Combined efficacy of acamprose and disulfiram						
Switzerland (Besson et al., 1998) ²³	110 (Acamprose: 31, placebo: 33; Acamprose + disulfiram: 24; placebo + disulfiram: 22)	100	12/12	ABW ^a	NR ^e	Acamprose: 25 ^d , Placebo: 5; Acamprose + disulfiram: NR; placebo + disulfiram: NR
						Acamprose: 40%, Placebo: 21%; Acamprose + disulfiram: 55%; placebo + disulfiram: 31%

^aAll studies required detoxification, except that in Gual and Lebert (2001), acamprose was prescribed from the start of alcohol withdrawal, rather than after detox. Abbreviations: ABW = adjusted for body weight (1998 mg/g day ≥ 60 kg; 1332 mg/g day < 60 kg); NR = not reported.

^bDefined as the proportion of randomly assigned patients completing double-blind treatment without having a single drink.

^cDefined as the total number of days of complete abstinence or the percentage of abstinent days during the total possible duration of exposure to double-blind treatment.

^dDifference between acamprose and placebo groups, $p < .05$.

^eGlutamyltransferase level was the primary outcome measure in this study and was significantly lower in acamprose patients than in placebo patients after 3 months of treatment (1.4 ± 1.56 vs. 2.0 ± 3.19 % upper limit of normal, $p = .016$).

^fDifference between acamprose and placebo plus disulfiram subgroups vs. other subgroups, $p < .05$.

^gDifference between acamprose plus disulfiram vs. placebo, $p > .05$.

less than 6 months of treatment are designated as short-term, studies involving 6 months of treatment are designated as such, and studies involving a year or more of treatment are designated as long-term.

1.1. Overview of Research Methodology

1.1.1. Design. All of the studies discussed in this chapter were double-blind, placebo-controlled, parallel-group comparisons with random assignment of patients to treatments.

1.1.2. Admission Criteria. Unless otherwise noted, subjects were male or female outpatients, 18 to 65 years of age, who met the *Diagnostic and Statistical Manual* (DSM) criteria for alcohol dependence. Many of the trials also specified a baseline gamma-glutamyltransferase (GGT) level of at least twice the upper limit of normal (ULN). In addition, several studies specified an above-normal mean corpuscular volume (MCV) among inclusion criteria. Exclusion criteria included serious medical disorders, pregnancy, and use of medication likely to influence study outcomes. In all but two trials (Chick et al., 2000; Gual & Lehert, 2001), patients were required to be abstinent for a minimum of 5 days prior to random assignment and were admitted to the study immediately upon completing alcohol detoxification, which was often on an inpatient basis.

1.1.3. Dosing. Acamprosate was administered orally, typically in a 333-mg tablet on a three times per day dosing schedule. In earlier studies, dosing of acamprosate was usually adjusted by body weight in a standard manner: patients who weighed 132 lb or more ($\geq 60\text{ kg}$) received 1998 mg/day or identical placebo, and those who weighed less than 132 lb received 1332 mg/day (Table 1) (Barrius et al., 1997; Besson et al., 1998; Geerlings et al., 1997; Ladewig et al., 1993; Pelc et al., 1992; Poldrugo, 1997; Rousseaux et al., 1996; Sass et al., 1996; Whitworth et al., 1996). More recent studies used a fixed dose of 1998 mg/day (Chick et al., 2000; Gual & Lehert, 2001; Tempesta et al., 2000).

1.1.4. Research Assessments. Assessments were minimally performed at days 0, 30, 90, 180, 270, and 360, depending on study duration (see Table 1), as well as at 3-month intervals during posttreatment follow-up, during which no study medication was administered. The duration of posttreatment follow-up ranged from 0 to 12 months (see Table 1).

1.1.5. Outcomes. For most studies, outcome parameters included the rate of study completion, the rate of abstinence for the interval preceding each study visit, the rate of patients' completing the trial without having a single drink (rate of total abstinence), the time to any relapse of drinking, and the cumulative abstinence duration (CAD). In earlier studies, CAD was defined as the total number of days of complete abstinence; in later studies, it was defined as the percentage of abstinent days during the total possible duration of exposure to double-blind treatment. Drinking outcomes were typically determined by

a combination of self-report; clinical interview; measures of alcohol in blood, urine, or breath; and biological marker data. Some studies also employed a collateral informant to corroborate outcomes.

1.1.6. Definition of Nonabstinence. Patients who took a single drink, missed visits, or had a self-report that was discrepant with biological marker data or collateral report were categorized as nonabstinent for the entire corresponding rating interval.

1.1.7. Statistical Analyses. Primary end-point analyses were conducted under an intention-to-treat statistical plan that included any randomly assigned patient who had taken at least one dose of study medication and for whom data were available on at least one key efficacy variable.

1.1.8. Compliance. Treatment compliance was determined by counting returned pills at each study visit.

1.1.9. Adverse Drug Events. Treatment-related adverse events were determined by physical examination, laboratory evaluation, spontaneous complaints, and complaints elicited by a standardized questionnaire.

1.1.10. Psychosocial Treatments. All patients were offered the type and frequency of psychosocial treatment for alcoholism usually administered at the study site. All forms of behavioral therapy were generally permitted; there was no standardized program of behavioral intervention across the studies.

1.2. Short-Term Efficacy Studies

The efficacy of acamprosate in patients with alcohol dependence was first assessed in France in a single-center trial involving 85 patients with severe alcoholism (Lhuintré et al., 1985). Treatment success was defined as complete abstinence during the 3-month study, as determined by clinical interview, a GGT level within the normal range, and decreased MCV. The success rate was significantly higher among acamprosate-treated patients compared with placebo-treated patients (61% vs. 32%).

In the first multicenter trial, Lhuintre et al. (1990) evaluated the effect of acamprosate on biological markers of alcohol intake in 569 alcohol-dependent patients, using the GGT level as the primary end point. All patients received a fixed dose of acamprosate (1332mg/day) or matched placebo. Patients treated with acamprosate exhibited GGT levels significantly lower than those of placebo patients (1.4 ± 1.56 vs. $2.0 \pm 3.19 \text{ } \mu\text{ULN}$, $p = .016$) after 3 months of treatment. Acamprosate appeared to exhibit dose-related effects; patients with a normal GGT level at 3 months had a lower initial body weight than those with an abnormal GGT level at 3 months. No weight-specific differences in GGT level were seen among placebo-treated patients.

In a single-center study conducted by Rousseaux et al. (1996), 127 patients with a DSM-III-R (APA, 1987) diagnosis of either alcohol abuse or alcohol dependence were randomly assigned to 3 months of double-blind treatment with acamprosate or placebo following completion of 2 weeks of inpatient detoxification. Medication dosing was determined by body weight (Table 1) and given on a twice daily dosing schedule to those in the low dose/low body weight condition. The authors suggested that the failure of acamprosate to separate from placebo in this study may have been due to several factors. First, the single success criterion of 3 months of complete abstinence may have been unreasonably stringent for a patient population whose degree of alcohol dependence initially required a 2-week inpatient detoxification. Second, the twice daily dosing schedule in the low-dose/low body weight condition may have been subtherapeutic, given the low absorption of acamprosate (Wilde and Wagstaff, 1997).

Pelc et al. (1997) compared two doses of acamprosate (1332 mg/day and 1998 mg/day) and placebo among 188 patients in a 3-month, multicenter, double-blind, placebo-controlled trial. All participants in the study weighed >60kg and were randomly assigned to one of three treatment groups (Table 1). Drinking diaries were reviewed, and urine alcohol levels were assessed at each study visit. The estimated rate of compliance was 95%, based on returned pill counts. Study completion rate, CAD, relapse rate, time to first relapse, and rate of complete abstinence were higher in the acamprosate treatment groups than in the placebo group. The higher dose of acamprosate exhibited a trend toward better outcome compared with the lower dose, a difference that was likewise reflected in GGT values.

1.3. Six-Month Efficacy Studies

Pelc et al. (1992) conducted a 6-month, multicenter trial among 102 patients to evaluate the efficacy of acamprosate under conditions typical of clinical practice. Significantly more acamprosate patients than placebo patients completed the trial and were continuously abstinent; acamprosate patients also had longer CADs than placebo patients. Mean GGT values confirmed drinking data and showed significantly greater improvement from baseline in acamprosate patients compared with placebo patients. Thus, this more naturalistic trial corroborated earlier reports suggesting that acamprosate improved abstinence rates and treatment retention. In the 6-month posttreatment follow-up phase, 13 of 55 acamprosate patients and 2 of 47 placebo patients remained completely abstinent.

Ladewig et al. (1993) evaluated acamprosate efficacy in 61 psychiatric patients with severe alcohol dependence in a 6-month study with a 6-month period of posttreatment follow-up. Patients treated with acamprosate exhibited a significantly greater CAD and rate of abstinence at day 30, and these differences were maintained throughout the trial; however, patient attrition reduced statistical significance. Likewise, survival analyses suggested that there was

a higher proportion of abstinent patients in the acamprosate group at the end of treatment and throughout the follow-up phase, although differences did not reach statistical significance in this reduced sample.

Geerlings et al. (1997) studied the efficacy of acamprosate among 262 patients recruited from 22 detoxification clinics in Belgium, the Netherlands, and Luxembourg. In the 6-month treatment phase of the study, the acamprosate group displayed a significantly longer mean time to first drink, a greater CAD, a higher percentage of abstinent patients at each study visit, and a greater likelihood of remaining abstinent. Rate of medication compliance was $\geq 86\%$. More patients in the acamprosate group completed treatment, and on average, these patients also remained in treatment longer than placebo-treated patients. However, only 56 of 262 patients (21%) completed the 6-month post-treatment follow-up. This high rate of posttreatment attrition was probably due to the limited amount of counseling received by patients during this period; on average, study subjects had only 20 minutes of contact with their clinician per month of follow-up. The authors recommended that future posttreatment follow-up studies focus more on motivation and prevention of drop out.

In a study by Poldrugo (1997), 246 participants in community-based outpatient alcoholism rehabilitation programs were randomly assigned to either acamprosate or placebo for 6 months. A subset of patients in each treatment group (acamprosate, 19.7%; placebo, 21.8%) elected to receive concomitant disulfiram. Compared with placebo, acamprosate was associated with a significantly higher rate of study completion, a higher rate of abstinence, a longer time to relapse, and a greater CAD. These effects were reflected in a lower rate of abnormal GGT levels in acamprosate patients during the treatment period. Outcomes did not differ between patients who took disulfiram and those who did not. Measures of craving showed no treatment effects. Higher rates of treatment participation (49.1% vs. 33.8%) and longer mean CAD (167.70 ± 151.05 vs. 120.48 ± 146.82 days, $p = .01$) were associated with acamprosate compared with placebo during the 6 months of treatment and 6 months of posttreatment follow-up combined.

Chick et al. (2000) conducted a 6-month efficacy study ($N = 581$) at 20 treatment centers in the United Kingdom in which patients received a fixed dose of acamprosate (1998 mg/day) or identical placebo. Although acamprosate appeared to decrease craving at 2 and 4 weeks, treatment effects were not observed for rate or duration of abstinence. Furthermore, subset analyses did not reveal any differences in treatment response among subpopulations of patients. It should be noted, however, that there was a long interval (up to 56 days) between detoxification and study randomization, and many patients (32%) were not abstinent at day 1 of treatment. Compliance was poor, and the treatment completion rate was very low (35%).

Tempesta et al. (2000) studied the efficacy of acamprosate in 246 outpatients recruited from 18 centers in southern Italy (330 patients began the study, and 25% discontinued). Patients participated in a comprehensive outpatient alcoholism treatment program and received a fixed dose of acamprosate (1998 mg/day) or

identical placebo (Table 1). The mean rate of medication compliance was >77% by returned pill count. Patients treated with acamprosate had significantly lower relapse rates, longer time to relapse, a higher rate of total abstinence, and a longer CAD than patients treated with placebo. Acamprosate modestly reduced alcohol consumption in nonabstinent patients, suggesting enhanced control over consumption. Acamprosate did not appear to affect craving.

Gual and Lehert (2001) evaluated the efficacy of acamprosate administered from the first day of outpatient detoxification (instead of after completion of detoxification and a minimum of 5 abstinent days prior to randomization, as per most European studies). The rationale for this strategy was to expose patients, who were likely to be rapid dropouts, to treatment and to reach steady-state levels of acamprosate, which take 5 days to achieve (Saivin et al., 1998), at about the time detoxification was completed, to achieve an optimal early effect. Two hundred ninety-six outpatients were recruited from 11 centers in Spain and treated with two 333 mg tablets of acamprosate or identical placebo three times daily for 6 months. Groups did not differ in mean detoxification time, change in Clinical Institute Withdrawal Assessment for Alcohol score, or frequency of use of detoxification medication. However, acamprosate patients had a significantly longer CAD than placebo patients, which was corroborated by GGT.

1.4. Long-Term Efficacy Studies

In a 12-month study with a 6-month follow-up phase, Barrias et al. (1997) evaluated the efficacy of acamprosate among 302 patients from nine centers. In the treatment phase, overall medication compliance was 87%, and the rate of total abstinence and the proportion of patients abstinent at each study visit were consistently higher in the acamprosate group than in the placebo group. Acamprosate-treated patients also had significantly longer CADs and latency to relapse than patients treated with placebo. During the 6-month follow-up, the proportion of abstinent patients on acamprosate gradually decreased relative to placebo; however, during the entire period of 540 days of treatment and posttreatment follow-up, mean CAD was significantly longer among acamprosate patients than placebo patients (225.1 ± 210.6 vs. 172.7 ± 198.7 days, $p = .025$). Mean GGT level decreased in both groups, and there was a numerically lower mean value in acamprosate patients, which corresponded with alcohol-drinking data. Acamprosate did not appear to affect measures of psychological dependence, physiological dependence, or craving.

In a trial involving 272 patients recruited from 12 outpatient psychiatry clinics, Sass et al. (1996) assessed the efficacy of acamprosate during 48 weeks of treatment and 48 weeks of posttreatment follow-up. Throughout the treatment phase, overall medication compliance was $\geq 94\%$, and acamprosate was associated with a significantly higher continuous rate of abstinence (43% vs. 21%, log rank $p = .005$) and a higher duration of abstinence compared with placebo (224 vs. 163 days, or 62% vs. 45% days abstinent; $p < .001$). In the follow-up

phase, significantly more acamprosate patients than placebo patients remained abstinent (39.9% vs. 17.3%, $p = .003$). Across the entire 2-year study, CAD was significantly longer in the acamprosate group than in the placebo group (54% vs. 35% abstinent days, $p = .001$).

Whitworth et al. (1996) also studied the efficacy of acamprosate in a 1-year study with an additional year of posttreatment follow-up. Of the 448 patients who took at least one dose of study medication, 179 (40%) completed the treatment phase, and 148 (33%) completed the follow-up phase. Survival analyses showed that the proportion of patients that remained abstinent was higher in the acamprosate group than in the placebo group throughout 1 year of treatment ($p = .007$). Acamprosate continued to show an advantage over placebo through the follow-up period; 27 acamprosate-treated patients (11.9%) and 11 placebo-treated patients (4.9%) remained continuously abstinent for 2 years. Mean CAD was significantly greater with acamprosate than with placebo across the entire study (230.8 ± 259.1 vs. 183.0 ± 235.2 days, $p = .039$).

Paille et al. (1995) assessed the dose-dependent effects of acamprosate in 538 patients from 31 centers in France. Patients were randomly assigned to receive acamprosate, 1998 mg/day ($N=173$), 1332 mg/day ($N=185$), or placebo ($N=177$), regardless of body weight. Following a 1-year, double-blind, treatment phase, patients entered a 6-month single-blind placebo phase (i.e., they were unaware that placebo had been substituted for acamprosate) to assess the effect of drug withdrawal on outcome. At all assessment points, the percentage of patients continuously abstinent was highest in the 1998-mg/day group and lowest in the placebo group. Dose-dependent effects also were observed for time to first relapse, treatment retention, CAD, and rate of abstinence at the 18-month follow-up visit. Mean GGT values were not sensitive to dose effects, but the rate of normal GGT levels was significantly higher in acamprosate groups than in placebo groups at 6 and 12 months. Craving did not show a dose effect and was not substantially changed by acamprosate. There was no evidence of increased risk of relapse following drug withdrawal under single-blind conditions.

In a 12-month, multicenter, double-blind, placebo-controlled study among 110 detoxified outpatients, Besson et al. (1998) evaluated the safety and efficacy of acamprosate administered alone or in combination with disulfiram. Disulfiram was administered open-label by request of the patients; 22 of 55 placebo patients and 24 of 55 acamprosate patients received the drug. Patients requesting disulfiram had significantly greater baseline severity of dependence, craving, and drinking-related functional impairment, as well as longer duration of alcohol dependence, compared with patients who did not choose disulfiram. Because medical personnel dispensed disulfiram tablets on a daily basis, disulfiram patients received additional interpersonal support and cognitive reinforcement of abstinence relative to other patients in the study. Acamprosate was dosed according to body weight (Table 1).

Patients who received acamprosate exhibited significantly higher abstinence rates than placebo patients after 30 days of treatment (73% vs. 43%, $p = .019$), as well as at the end of treatment (Table 1). The mean CAD also was significantly

greater in acamprosate patients than in placebo patients (136.9 ± 147.5 vs. 74.7 ± 107.9 days, or 40% vs. 21%, $p = .013$). Placebo-treated patients had GGT values significantly higher than those of acamprosate-treated patients at days 30, 90, and 180. Analysis of results stratified for the concomitant use of disulfiram (Table 1) showed a significantly longer CAD in the subgroup that received both medications, whereas patients who received neither medication had the briefest CAD. Patients who received acamprosate alone exhibited a cumulative abstinence comparable to that of patients who received disulfiram alone. Craving was not affected by treatment. No adverse interactions between acamprosate and disulfiram occurred, and neither medication dependence nor rebound drinking were reported during a 1-year follow-up period.

1.5. Safety

Across the double-blind, placebo-controlled, clinical trials, the rate of early terminations due to drug-related adverse events did not differ between acamprosate- and placebo-treated patients. Adverse events associated with acamprosate tended to be mild and transient. Mild diarrhea or loose stools was the only adverse event that consistently occurred more frequently with acamprosate than with placebo and affected approximately 10% of patients. In a study by Paille et al. (1995), the proportion of patients that experienced diarrhea appeared to be dose-dependent: 7.5% of patients who received 1332 mg/day of acamprosate reported diarrhea versus 12% of patients who received 1998 mg/day (the rate of diarrhea among placebo patients was 3.4%). However, no dose effect on adverse events was noted in a second dose-response study by Pelc et al. (1997).

In conjunction with the excellent safety profile observed in clinical trials, several pharmacokinetic and pharmacodynamic characteristics make acamprosate well suited for treating of a broad population of alcohol-dependent patients. First, it has no abuse potential and appears to have minimal pharmacological effects, apart from those involved in reducing the rate of drinking relapse (Grant et al., 1989). Second, it does not appear to interact with ethanol or compounds commonly prescribed for treating alcoholism (e.g., disulfiram, antidepressants, anxiolytics, neuroleptics, or hypnotics) (Durbin et al., 1996), nor does it appear to interact adversely with naltrexone (Mason et al., under review). Third, it can be administered to patients with liver dysfunction, since it does not undergo significant hepatic metabolism (it should not be used in patients with renal insufficiency, however) (Wilde and Wagstaff, 1997). Finally, acamprosate does not cause acute opioid withdrawal symptoms in patients using opioids; thus, it may be useful for methadone-maintained patients dependent on both alcohol and narcotics.

2. Commentary

Overall, double-blind, placebo-controlled trials published to date have suggested that acamprosate is a safe and well-accepted therapy that prolongs abstinence

and reduces the rate of relapse among alcohol-dependent patients. Although effect sizes varied from study to study, both primary and secondary efficacy outcomes (e.g., GGT levels) typically favored acamprosate over placebo. Differences in abstinence rates between acamprosate patients and placebo patients generally emerged within the first 30 to 90 days of treatment, were sustained for up to 1 year of treatment, and were maintained for as long as 12 months after treatment (Barrius et al., 1997; Geerlings et al., 1997; Ladewig et al., 1993; Pelc et al., 1992; Poldrugo et al., 1997; Sass et al., 1996; Tempesta et al., 2000; Whitworth et al., 1996). The compound did not appear to reduce craving relative to placebo. Thus, although acamprosate is commonly referred to as an anticraving agent, it is more accurately described as a relapse-prevention drug.

Acamprosate failed to demonstrate a significant effect on primary outcome measurements relative to placebo in 2 of the 16 published studies. However, both of these investigations had unusual and potentially confounding design characteristics. For example, the study conducted by Rousseaux et al. (1996) assessed treatment success using a single, narrowly defined outcome criterion and used possibly insufficient dosing for some patients. The second inconclusive investigation (Chick et al., 2000) postponed therapy until up to 2 months after detoxification, so that a third of the subjects had relapsed by day 1 of double-blind treatment.

Acamprosate, it is presumed, supports abstinence and reduce relapse in alcohol dependence by normalizing central NMDA receptor hyperactivity associated with chronic heavy alcohol use and states of withdrawal (Littleton et al., 1995; Naassila et al., 1998; Zeise et al., 1993). Hence, abstinence-induced NMDA receptor dysregulation would not be expected in nonabstinent subjects. Consistent with these preclinical data, the clinical efficacy of acamprosate as a relapse prevention agent appears to be contingent on an initial period of abstinence. Other than a brief baseline period of abstinence, no clear pattern of predictors for acamprosate treatment response has been identified.

In contrast to the recent U.S. trial, which mandated a standardized behavioral treatment program at all participating sites (Mason & Goodman, 1997), the European multicenter studies allowed each site to provide the behavioral therapy routinely offered in its setting. The results of these highly variable studies suggest that acamprosate can be used to good effect with a diverse range of concomitant psychosocial interventions.

Acamprosate appears to be useful for a broad range of alcohol-dependent patients. In addition to being generally safe and well tolerated, acamprosate is suitable for use in patients with liver dysfunction (Wilde and Wagstaff, 1997) or concomitant opioid dependence. It is also safe for patients receiving other medications used in treating of alcohol dependence, including disulfiram and naltrexone (Besson et al., 1998; Mason et al., under review). The efficacy of combination pharmacotherapy with acamprosate and naltrexone is under evaluation in a number of studies and may expand the options for treatment-refractory patients. Finally, the high rates of medication compliance typically reported across studies support the acceptability of acamprosate and the thrice daily dosing schedule in outpatients with alcohol dependence.

In summary, acamprosate modestly but reliably promotes abstinence and prevents drinking relapse among alcohol-dependent patients. Its safety, tolerability, and compatibility with a wide spectrum of concomitant pharmacological and behavioral treatments make it well suited for treating of alcohol dependence.

Drug names: acamprosate (Campral), disulfiram (Antabuse), naltrexone (ReVia).

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References

- American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., rev. Washington, DC: American Psychiatric Association.
- Barriás, J.A., Chabac, S., Ferreira, L., Fonte, A., Potgieter, A.S., & Teixeira de Sousa, E. (1997). Acamprosate: Multicenter Portuguese efficacy and tolerance evaluation study. *Psiquiatria Clinica* 18, 149–160.
- Besson, J., Aeby, F., Kasas, A., Lehert, P., & Potgieter, A. (1998). Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: A controlled study. *Alcoholism, Clinical and Experimental Research* 22, 573–579.
- Chick, J., Hewlett, H., Morgan, M.Y., & Ritson, B. (2000). United Kingdom Multicentre Acamprosate Study (UKMAS): A 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol and Alcoholism* 35, 176–187.
- Durbin, P., Hulot, T., Chabac, S. (1996). Pharmacodynamics and pharmacokinetics of acamprosate: An overview. In M. Soyka (ed.), *Acamprosate in Relapse Prevention of Alcoholism*. Berlin, Germany: Springer-Verlag.
- Geerlings, P.J., Ansoms, C., & van den Brink, W. (1997). Acamprosate and prevention of relapse in alcoholics. *European Addiction Research* 3, 129–137.
- Grant, K.A., & Woolverton, W.L. (1989). Reinforcing and discriminative stimulus effects of Ca-acetyl homotaurine in animals. *Pharmacology, Biochemistry and Behavior* 32, 607–611.
- Gual, A., & Lehert, P. (2001). Acamprosate during and after acute alcohol withdrawal: A double-blind, placebo-controlled study in Spain. *Alcohol and Alcoholism* 36(5), 413–418.
- Ladewig, D., Knecht, T., Lehert, P., & Fendl, A. (1993). Acamprosate: A stabilizing factor in long-term withdrawal of alcoholic patients. *Therapeutische Umschau* 50, 182–188.
- Lhuître, J.P., Daoust, M., Moore, N.D., Saligaut, C., Boismare, F., Chretien, P., Tranl, G., & Hillemand, B. (1985). Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. *Lancet* 1, 1014–1016.
- Lhuître, J.P., Moore, N., Tran, G., Steru, L., Lancronon, S., Daoust, M., Parot, P., Ladure, P., Libert, C., Boismare, F., & Hillemand, B. (1990). Acamprosate appears to decrease alcohol intake in weaned alcoholics. *Alcohol and Alcoholism* 25, 613–622.
- Littleton, J. (1995). Acamprosate in alcohol dependence: How does it work? *Addiction* 90, 1179–1188.

- Mason, B.J., & Goodman, A.M. (1997). *Brief Intervention and Medical Compliance Procedures Therapist's Manual*. New York: Lipha Pharmaceuticals.
- Mason, B.J., Goodman, A.M., Dixon, R.M., Abdel Hameed, M.H., Hulot, T., Wesnes, K., & Hunter, J.A. (under review). A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone.
- Mason, B.J., & Ownby, R.L. (2000). Acamprosate for the treatment of alcohol dependence: A review of double-blind, placebo-controlled trials. *CNS Spectrums* 5, 58–69.
- Naassila, M., Hammoumi, S., Legrand, E., Durbin, P., & Daoust, M. (1998). Mechanism of action of acamprosate. Part 1. Characterization of spermidine-sensitive acamprosate binding site in rat brain. *Alcoholism, Clinical and Experimental Research* 22, 1–8.
- Paille, F.M., Guelfi, J.D., Perkins, A.C., Royer, R.J., Steru, L., & Parot, P. (1995). Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. *Alcohol and Alcoholism* 30, 239–247.
- Pelc, I., Le Bon, O., Verbanck, P., Lehert, P.H., Opsomer, L. (1992). Calcium acetyl homotaurinate for maintaining abstinence in weaned alcoholic patients: A placebo controlled double-blind multi-centre study. In C. Naranjo & E. Sellers (eds.), *Novel Pharmacological Interventions for Alcoholism*. New York: Springer-Verlag, pp. 348–352.
- Pelc, I., Verbanck, P., Le Bon, O., Gavrilovic, M., Lion, K., & Lehert, P. (1997). Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: A 90-day placebo-controlled dose-finding study. *British Journal of Psychiatry* 171, 73–77.
- Poldrugo, F. (1997). Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. *Addiction* 92, 1537–1546.
- Rousseaux, J.P., Hers, D., & Ferauge, M. (1996). Does acamprosate diminish the appetite for alcohol in weaned alcoholics? *Journal de Pharmacie de Belgique* 51, 65–68.
- Saivin, S., Hulot, T., Chabac, S., Potgieter, A.S., Durbin, P., & Houin, G. (1998). Clinical pharmacokinetics of acamprosate. *Clinical Pharmacokinetics* 35, 331–345.
- Sass, H., Soyka, M., Mann, K., & Zieglgansberger, W. (1996). Relapse prevention by acamprosate: Results from a placebo-controlled study on alcohol dependence. *Archives of General Psychiatry* 53, 673–680.
- Tempesta, E., Janiri, L., Bignamini, A., Chabac, S., & Potgieter, A. (2000). Acamprosate and relapse prevention in the treatment of alcohol dependence: A placebo-controlled study. *Alcohol and Alcoholism* 35, 202–209.
- Whitworth, A.B., Fischer, F., Lesch, O.M., Nimmerrichter, A., Oberauer, H., Platz, T., Potgieter, A., Walter, H., & Fleischhacker, W.W. (1996). Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* 347, 1438–1442.
- Wilde, M.I., & Wagstaff, A.J. (1997). Acamprosate: A review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification. *Drugs* 53, 1038–1053.
- Zeise, M.L., Kasparov, S., Capogna, M., & Zieglgansberger, W. (1993). Acamprosate (calcium acetyl-homotaurinate) decreases postsynaptic potentials in the rat neocortex: Possible involvement of excitatory amino acids receptors. *European Journal of Pharmacology* 231, 47–52.

Advances in the Use of Naltrexone

An Integration of Preclinical and Clinical Findings

Stephanie S. O'Malley and Janice C. Froehlich

1. Introduction

Naltrexone, a competitive opioid antagonist, was approved in 1994 for use in treating alcohol dependence following a period of systematic research on how the endogenous opioid system is implicated in the reinforcing effects of alcohol and how agents that modify endogenous opioid activity alter alcohol drinking. Various lines of preclinical evidence demonstrate that alcohol-induced activation of the endogenous opioid system is a neurobiological mechanism that is functionally involved in alcohol reinforcement and alcohol drinking behavior (for reviews, see Froehlich & Li, 1993, 1994). First, neurobiological studies have demonstrated that alcohol increases activity in the opioid peptide system of both rodents and humans (Froehlich, 1995; Gianoulakis, 1990; Gianoulakis, Hutchison, & Kalant, 1988; Krishnan-Sarin, Wand, Li, Portoghesi, & Froehlich, 1998; Li, Li, & Froehlich, 1998; Seizinger, Bovermann, Maysinger, Hollt, & Herz, 1983). The second line of evidence for functional involvement of the opioid system in mediating alcohol drinking behavior is derived from genetic studies which indicate that a genetic predisposition toward alcohol drinking is associated with increased sensitivity of the opioid system to alcohol in both rodents and humans (De Waele, Papachristou, & Gianoulakis, 1992; Froehlich, 1995; Gianoulakis, De Waele, & Thavundayil, 1996; Jamensky & Gianoulakis, 1997; Krishnan-Sarin, Wand, Li, Portoghesi, & Froehlich, 1998; Li, Li, & Froehlich 1998). Finally, pharmacological studies indicate that both nonselective opioid

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receptor antagonists, such as naloxone and naltrexone, and antagonists that are selective for the mu and delta opioid receptor subtypes decrease alcohol self-administration in rodents and monkeys in a variety of experimental conditions (Altshuler, Phillips, & Feinhandler, 1980; Badia-Elder, Mosemiller, Elder, & Froehlich, 1999; Froehlich, 1995; Froehlich, Harts, Lumeng, & Li, 1990; Froehlich, Zweifel, Harts, Lumeng, & Li, 1991; Herz, 1997; Hubbell et al., 1986, 1991; Hubbell & Reid, 1990; Krishnan-Sarin, Jing et al., 1995a; Krishnan-Sarin, Portoghese, Li, & Froehlich, 1995b; Krishnan-Sarin et al., 1998; Le, Poulos, Quan, & Chow, 1993; Volpicelli, Davis, & Olglin, 1986; Weiss, Mitchiner, Bloom, & Koob, 1990). Based on preclinical findings, Volpicelli and colleagues first tested the effects of naltrexone on alcohol consumption in human subjects (Volpicelli, Alterman, Hayashida, & O'Brien, 1992; Volpicelli, O'Brien, Alterman, & Hayashida, 1990), and O'Malley and colleagues (O'Malley et al., 1992) replicated and extended this work to test the effects of naltrexone in combination with two forms of psychotherapy. Both studies demonstrated that naltrexone is effective in reducing the risk of heavy drinking in alcohol-dependent patients.

Subsequent to the approval of naltrexone, research on opiate antagonists has expanded greatly. This review will provide a summary of the preclinical and clinical evidence, related to the optimal use of naltrexone as a treatment for alcohol dependence. A defining feature of alcohol dependence is loss of control over alcohol use, specifically over the decision about whether or not to drink and over the amount of alcohol consumed once drinking is initiated. Both of these aspects are potential targets for pharmacological interventions. In section 2, we review evidence about the putative neurobiological mechanisms of action for naltrexone in altering drinking behavior. Section 3 discusses the effects of naltrexone on these different aspects of alcohol drinking, including the ability to resist drinking (i.e., to maintain abstinence), as well as the likelihood of relapse to heavy drinking, and how naltrexone may alter patterns of drinking within a drinking occasion and across days. In section 4, we discuss issues related to dose and dosing strategies. The fifth section examines predictors of response to naltrexone, including individual patient characteristics as well as program characteristics, and the final section presents new research on the combined use of naltrexone and other pharmacotherapies. Throughout the chapter, information from both preclinical and clinical studies is reviewed to identify ways to potentially maximize the effectiveness of naltrexone as a treatment for alcohol use disorders.

2. Mechanisms of Action of Naltrexone

One of the most potent effects of alcohol that contributes to continued and repeated bouts of alcohol drinking is induction of euphoria and feelings of well-being that may be mediated by alcohol-induced release of beta-endorphin. Beta-endorphin is an endogenous opioid peptide that acts like morphine and induces euphoria (Koob & Bloom, 1983). In humans, there is a strong correlation between feelings of well-being/euphoria and plasma levels of beta-endorphin,

and peripheral administration of beta-endorphin produces mood elevation (Akil et al., 1984; Henry, 1982; Janal, Colt, Clark, & Glusman, 1984). Naloxone and naltrexone are nonspecific opioid receptor antagonists that block the action of beta-endorphin at the level of the opioid receptors (for a review, see Froehlich, 1997) and act to reduce the positively reinforcing or euphoriant effects of alcohol (Swift, Whelihan, Kuznetsov, Buongiorno, & Hsuing, 1994; Volpicelli, Watson, King, Sherman, & O'Brien, 1995) as well as the desire to drink and subjective craving for alcohol (Anton et al., 1999; Davidson, Palfai, Bird, & Swift, 1999; McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000; O'Malley, Jaffe, Rode, & Rounsville, 1996; O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002). It is not surprising, therefore, that preclinical studies have found that naloxone and naltrexone reduce alcohol intake in a variety of conditions involving acute consumption, chronic consumption, and relapse.

Clearly, activation of opioid receptors is important for continuation of alcohol drinking and reinitiation of drinking following termination of drinking (relapse), and these actions are probably mediated by an interaction between opioid peptides and dopamine (DA) in the brain. Preclinical studies have demonstrated that alcohol, like many other drugs of abuse, increases dopamine (DA) release in the nucleus accumbens (Di Chiara, Acquas, & Carboni, 1992; Di Chiara & Imperato, 1988; Weiss, Lorang, Bloom, & Koob, 1993), a terminal region of the mesolimbic DA system that is thought to be involved in the reinforcing effects of alcohol and other drugs of abuse (Koob, 1992; Koob et al., 1998; Weiss et al., 1992, 1993; Wise, 1996). Various lines of preclinical evidence indicate that opioid peptides mediate alcohol-induced DA release from the accumbens, and it has been demonstrated that naloxone and naltrexone block alcohol-induced DA release from the accumbens and other areas of the brain reward system (Benjamin, Grant, & Pohorecky, 1993; Gonzales & Weiss, 1998; Widdowson & Holman, 1992). For instance, Gonzales and Weiss (1998) demonstrated that naltrexone treatment effectively reduces the ability of alcohol drinking to increase dopamine levels in the accumbens in rats. Importantly, in addition to alcohol itself, expectancy of alcohol, it has been shown, moderately increases DA release in the accumbens (Gonzales & Weiss, 1998; Katner, Kerr, & Weiss, 1996; Katner & Weiss, 1999; Weiss et al., 1993), and naltrexone has been reported to block cue-induced reinstatement of alcohol seeking in an animal model of alcohol relapse (Katner & Weiss, 1999). Taken together, these preclinical results suggest that alcohol drinking and cue-induced alcohol relapse are mediated, in part, by opioid-induced alterations of DA release in the mesolimbic DA system.

Although it has been suggested that naloxone and naltrexone may reduce alcohol drinking by inducing nausea, recent findings in the preclinical literature do not support this view. A naloxone derivative that does not enter the systemic circulation (methylnaloxonium), when injected directly into the nucleus accumbens, significantly reduces operant alcohol self-administration in rats (Heyser, Roberts, Schulteis, & Koob, 1999). We have recently found that when a delta opioid receptor antagonist is injected directly into the nucleus accumbens or into the ventral tegmental area which projects to the accumbens,

alcohol consumption is reduced in rats given scheduled access to alcohol (McCullough, Mosemiller, Portoghesi, & Froehlich, 1999; McCullough, Portoghesi, & Froehlich, 2000; McCullough, Mosemiller, Zhou, Portoghesi, & Froehlich, 1998). In all of these studies involving site-specific administration of opioid antagonists directly into the brain reward system, the reduction in alcohol intake was due to early termination of alcohol drinking or operant responding for alcohol. In human subjects, studies using fixed doses of alcohol (McCaul et al., 2000) reported nausea in interaction with naltrexone; however, in a self-administration paradigm in which alcohol-dependent subjects controlled the amount of alcohol consumed, naltrexone reduced alcohol self-administration without producing nausea (O'Malley et al., 2002).

3. Effects of Drinking Behavior

3.1. *Maintenance of Abstinence*

Individuals with alcohol dependence often find it difficult to maintain abstinence once it is achieved. Although the effects of naltrexone in preventing sampling of alcohol have not been pronounced in individual clinical trials, there have been trends in these data. Two recent meta-analyses of published naltrexone studies found a significant advantage of naltrexone over placebo in the maintenance of abstinence with effect sizes of .12 (Kranzler & Van Kirk, 2001) and .10 (Streeton & Whelan, 2001) in 12-week studies. In the Kranzler and Van Kirk analysis of nine published placebo controlled randomized trials (Anton et al., 1999; Chick et al., 2000; Hersh, Van Kirk, & Kranzler, 1998; Kranzler, Modesto-Lowe, & Nuwayser, 1998; Kranzler, Modesto-Lowe, Van Kirk, & J, 2000; O'Malley et al., 1992; Volpicelli et al., 1992,1997), this represented a 12% improvement over placebo in continuous abstinence rates, which is comparable to the effects of acamprosate, a medication more widely appreciated for its effects on alcohol abstinence, and is comparable to the 12% advantage of the nicotine patch over placebo in the maintenance of abstinence from smoking (Kranzler & Van Kirk, 2001). Since this meta-analysis, five double-blind, placebo-controlled studies (Heinala, Alho, Kianma, Lonnqvist, & Kuoppasalmi, 2001; Krystal et al., 2001; Monterosso et al., 2001; Monti et al., 2001; Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001) have been published. Morris and colleagues studied 111 alcohol-dependent subjects who were randomized to naltrexone 50 mg or placebo for 12 weeks in conjunction with weekly group psychotherapy. In this study, which did not require abstinence prior to initiation of therapy, naltrexone did not alter time to first drink. However, among those who completed the 12-week trial, 21% (8/38) of the naltrexone patients remained continuously abstinent compared to 12% (4/33) of the placebo patients. The remaining studies did not present data on continuous abstinence rates.

The number or percentage of days abstinent (or the converse, number or percentage of days drinking) is another measure that can reflect the potential of

a medication to support abstinence. Naltrexone had a significant effect on this measure with a 19% improvement noted over placebo in the Kranzler and VanKirk meta-analysis (Kranzler & Van Kirk, 2001). Two of the five more recent randomized controlled clinical trials (RCTs) also report this outcome. In the Morris study, the percentage of days abstinent was somewhat higher in the naltrexone group (75% vs. 64%) in an analysis of completers; this statistic was not reported for the intent to treat sample (Morris et al., 2001). In the Veterans Affairs (VA) Naltrexone Cooperative Study, the difference in the percentage of drinking days was not significant for comparisons of naltrexone to placebo in either the short-term analysis of 13-week outcomes or the 52-week analysis. Given that meta-analytic results find an advantage of naltrexone over placebo on continuous abstinence and percentage of days abstinent, future studies should include these measures routinely to better delineate the effects of naltrexone in particular patient populations and in conjunction with different behavioral interventions.

To understand how naltrexone may support abstinence, investigators have examined how naltrexone alters responses to situations that have been implicated in resumption of drinking, such as stress and/or negative affect in humans (Brown, Vik, Patterson, Grant, & Schuckit, 1995; Hore, 1971) and alcohol-related cues (Ludwig, Wikler, & Stark, 1974; Monti et al., 1993; Staiger & White, 1991). In the animal literature, one animal model, the reinstatement model (Stewart & de Wit, 1987), is particularly relevant to reinitiation of drinking following a period of abstinence. In this model, the ability of alcohol ("alcohol priming"), alcohol-related cues, or stressors to reinstate alcohol seeking or alcohol self-administration is examined in animals that have been trained to press a lever for administration of alcohol (intravenously or orally) and have then undergone extinction of the drug-reinforced behavior which occurs as a function of discontinuing alcohol administration.

With regard to alcohol-related cues, Katner and Weiss (1999) found that naltrexone reduced reinstatement of operant alcohol-seeking behavior induced by exposure to an alcohol-related cue (odor of alcohol), even though no alcohol was available for consumption during cue exposure. This finding has important implications for the design of clinical naltrexone treatment regimens for preventing alcohol relapse in humans. It is well known that environmental stimuli associated with alcohol availability can induce a strong craving for alcohol and can reinstate alcohol-seeking behavior in humans. The results of the pre-clinical study by Katner and Weiss (1999) suggest that administering naltrexone during abstinence may reduce alcohol craving and behaviors directed toward obtaining alcohol ("alcohol-seeking behavior") when alcohol-related cues are encountered during abstinence. These results support the findings of a recent clinical report that naltrexone, compared with placebo, reduced the number of alcohol-dependent patients who reported any urge to drink during exposure to alcohol-related cues in a cue reactivity paradigm (Monti et al., 1999).

With regard to the ability of alcohol itself to reinstate drinking in animals, Le and colleagues (Le et al., 1999) and Bienkowski and colleagues (Bienkowski,

Kostowski, & Koros, 1999) found that pretreatment with naltrexone blocked reinstatement of alcohol drinking induced by noncontingent alcohol priming following extinction. Although low dose naltrexone did not block the ability of stress to reinstate alcohol seeking following an extinction period (Le et al., 1999), work by Volpicelli and colleagues (Volpicelli et al., 1986) indicates that in the actively drinking animal, naltrexone can attenuate stress-induced increases in the amount of alcohol consumed.

The results of several preclinical studies using operant paradigms other than the reinstatement model indicate that naloxone and naltrexone did not eliminate the motivation to drink alcohol. Specifically, pretreatment with these opioid receptor antagonists did not eliminate initiation of alcohol drinking or "alcohol sampling" (Hyytia & Kianmaa, 2001; Schwarz-Stevens, Files, & Samson, 1992; Sivy, Calcagnetti, & Reid, 1982; Stromberg, Mackler, Volpicelli, & O'Brien, 2001). It should be noted, however, that animal and human studies differ with regard to several important factors. In animal studies, there is little else in the environment to distract the animal from the presentation of alcohol. Humans, on the other hand, encounter alcohol-related cues and alcohol access opportunities in the context of complex environmental stimuli. It would be interesting to design preclinical studies to explore the effect of naloxone or naltrexone on time to onset of alcohol drinking, pattern, and duration of drinking, and total consumption in environments that are bare (normal experimental rodent environments) compared with those that are rich with distracting stimuli. Another important difference between animal and human studies is that most alcoholics treated with naltrexone are trying to resist drinking, are thinking of the rewards associated with staying sober (family and self-satisfaction, job security, etc.), and are practicing strategies that they have learned to avoid using alcohol. Under these conditions, a modest suppressive effect of naltrexone on the motivation to drink alcohol may be amplified. Again, preclinical experiments could be designed to explore the effect of naltrexone on the motivation to drink and on alcohol consumption under conditions that reward the animal for avoiding alcohol or punish the animal for alcohol sampling. It would be interesting to determine whether naltrexone alters the strength of the contingencies needed to produce alcohol avoidance or a delay in time to onset of the first drink.

3.2. Relapse to Heavy Drinking

Difficulty resisting the first drink would not be an issue if it were not that individuals with alcoholism have difficulty limiting the amount of alcohol consumed once drinking is initiated. As a result, clinical investigators have considered relapse to heavy drinking one of the primary outcomes by which to evaluate the efficacy of naltrexone. Meta-analytic studies (Kranzler & Van Kirk, 2001; Streeton & Whelan, 2001) report that naltrexone results in a 14–16% reduction in relapse rates compared to placebo. Relapse to heavy drinking has been defined as drinking beyond some upper amount (e.g., five or six drinks

for men and four drinks for women) on a single day or any drinking across a specified number of days (e.g., 5–7 days). The RCTs published subsequent to these meta-analyses are generally consistent with the conclusions of earlier studies. Three studies found a significant advantage of naltrexone over placebo in the intent to treat analysis of time to first day of heavy drinking (Heinala et al., 2001; Monterosso et al., 2001; Morris et al., 2001), and one study found this effect in the completer sample (Monti et al., 2001). Although time to first day of heavy drinking (72.3 ± 36 vs. 62.4 ± 34) was longer and relapse rates (37.8% vs. 44.4%) were lower for naltrexone compared to placebo during the first 13 weeks of the VA Naltrexone Cooperative Study (Krystal et al., 2001), these differences were not significant. Across the 52-week treatment period, median time to relapse appears to favor long-term treatment with naltrexone (176 days) compared to short-term naltrexone (115 days) or placebo (104 days) (footnote, Table 4), but statistical tests of this relationship are not provided. Although the negative VA study is an important exception, the body of evidence from recent and past RCTs indicates that naltrexone can reduce the risk of heavy drinking, at least in subjects who are compliant with treatment.

Preclinical and human laboratory studies have been conducted that shed additional light on this question. One preclinical model of importance is the alcohol deprivation model in which the intake of alcohol is determined after prolonged periods of forced abstinence in animals with a history of alcohol experience. The alcohol deprivation effect (ADE), which refers to a temporary increase in alcohol consumption over baseline levels after periods of abstinence (Sinclair & Senter, 1967), has been found reliable and robust in rodents, can result in very large, transient, increases in alcohol intake (Heyser, Schulteis, & Koob, 1997; Holter & Spanagel, 1999; McKinzie et al., 1998; Rodd-Henricks et al., 2000; Sinclair, Walker, & Jordan, 1973; Spanagel, Holter, Allingham, Landgraf, & Zieglgansberger, 1996; Wolffgramm, Galli, Thimm, & Heyne, 2000; Wolffgramm & Heyne, 1995); and may reflect an increase in the reinforcing value of alcohol (Spanagel & Holter, 2000). Acute and/or intermittent treatment with low to moderate doses of naloxone or naltrexone prior to reexposure to alcohol following deprivation to it has been found to decrease the magnitude of the ADE in rodents (Holter & Spanagel, 1999) and monkeys (Kornet, Goosen, & Van Ree, 1991).

These preclinical findings agree well with the clinical results indicating that alcoholics who "slip" and drink alcohol while taking naltrexone consume less alcohol (O'Malley et al., 1992; Volpicelli et al., 1992). Subjects also reported that the "high" they experienced from alcohol while taking naltrexone was less than they had previously experienced when not taking naltrexone, was less than they had expected to experience (Volpicelli et al., 1995) and that their craving was lower (O'Malley et al., 1996). In laboratory studies, it has been found that naltrexone compared to placebo reduces the stimulating effects of alcohol, which may be considered reinforcing, and increases the sedating effects of alcohol (King, Volpicelli, Frazer, & O'Brien, 1997; Swift et al., 1994). Additional evidence that naltrexone attenuates the reinforcing effects of alcohol

comes from a study (McCaul et al., 2000) testing the effects of chronic dosing with three doses of naltrexone (placebo, 50 mg, 100 mg) in interaction with three doses of alcohol (0.0, 0.5, 1.0g/kg) in heavy drinkers. Decreased ratings of liking, best effects, and desire to drink were observed, particularly at the high doses of naltrexone and alcohol. Importantly, naltrexone reduces alcohol craving in laboratory studies of heavy drinkers and alcohol-dependent non-treatment-seeking subjects (Davidson et al., 1999; Davidson, Swift, & Fitz, 1996; McCaul et al., 2000; O'Malley et al., 2002).

3.3. Patterns of Drinking

Analyses of results from naltrexone clinical trials have focused on measures of time to first day of heavy drinking, often using survival analyses. In this approach, detailed information about subsequent days of drinking is not incorporated. Some studies suggest, however, that naltrexone may increase the length of time between a lapse in abstinence and a day of heavy drinking (O'Malley et al., 1992; Rubio, Jimenez-Arriero, Ponce, & Palomo, 2001), the time between nonabstinent days (Wang, 2000), the time from a day of heavy drinking to the next day of heavy drinking (Anton et al., 1999; Wang, 2000), and the percentage of heavy drinking days (Anton et al., 2001; Monti et al., 2001). The increased duration between days of drinking may explain, in part, the finding that naltrexone is associated with an increase in the percentage of days abstinent in many studies.

The preclinical literature provides an opportunity to examine more closely the effects of naltrexone on drinking patterns within a drinking session and across sessions. Within an individual drinking session, preclinical studies suggest that naloxone and naltrexone do not alter the onset of alcohol drinking in rats. Instead, they shorten the duration of the alcohol drinking session, that is, produce early termination of drinking once drinking has begun (Hyytia & Kiiianmaa, 2001; Schwarz-Stevens et al., 1992; Siviy et al., 1982; Stromberg et al., 2001). For instance, Hyytia and Sinclair (1993) showed that naloxone does not alter operant alcohol self-administration in rats during the beginning of the first scheduled drinking session in a scheduled alcohol access paradigm, but rather naloxone reduces alcohol self-administration later in the alcohol access session. Using a new animal operant self-administration paradigm, Sharpe and Samson (2001) have been able to examine the effects of naloxone on the motivation to drink alcohol as separate from consumption of alcohol by rats. They found that naloxone moderately suppressed the motivation to drink alcohol but that the effect was not statistically significant. In contrast, naloxone produced an earlier cessation of alcohol self-administration in the alcohol access session, that is, naloxone decreased alcohol intake by terminating alcohol drinking earlier in the session, thus decreasing the overall time spent drinking and the amount of alcohol consumed.

Across sessions, Stromberg and colleagues (1998) found that 30 and 60 days of intermittent naltrexone administration suppressed alcohol drinking by the rat

and that naltrexone-induced suppression of alcohol intake became greater over the time of chronic intermittent naltrexone administration. Hyytia and Sinclair (1993) also found increasing suppression of operantly self-administered alcohol consumption over several days. Interestingly, they reported that chronic intermittent naloxone treatment did not suppress the amount of alcohol operantly self-administered by rats at the beginning of a scheduled alcohol access period on the first day of naloxone treatment but alcohol self-administration during the beginning of the alcohol access period gradually declined during several days of naloxone treatment. These authors and others (Reid, 1996a) suggested that this reflects a learning phenomenon and that the rats are learning that consumption of alcohol is no longer reinforcing when consumed in the presence of naloxone or naltrexone.

In humans, we have tested the ability of naltrexone to modify alcohol consumption using a paradigm that models the effects of a lapse in abstinence on subsequent drinking (O'Malley et al., *in press*). Following 6 days of pretreatment with either naltrexone 50 mg daily or matching placebo, subjects were administered a priming drink of alcohol designed to raise blood alcohol levels to 0.03 g/dl, and craving was monitored for 40 minutes. Subjects then had the opportunity to consume eight additional drinks designed to raise blood alcohol levels by 0.015 g/dl or to receive \$3 for each drink not consumed during a 2-hour period. They were provided access to four of these drinks in each hour. Many of the findings of this study are consistent with the preclinical literature. First, although not statistically significant in this small study of 18 subjects, the number of drinks consumed on each day of the pretreatment period declined over time, paralleling the findings of Hyytia and Sinclair (1993). Regarding drinking behavior within the session, naltrexone treated subjects drank fewer drinks (1.9 ± 0.7 vs. 4.6 ± 0.9) and drank them more slowly. Interestingly, the differences between the naltrexone and placebo-treated subjects on the number of drinks consumed was most pronounced in the second hour of the drinking session. In the first hour, the number of drinks consumed was somewhat lower in the naltrexone group compared to the placebo group (1.3 ± 0.48 vs. 2.2 ± 0.43). However, only three of the eight naltrexone treated subjects continued drinking in the second hour in contrast to 8 of the 10 placebo-treated subjects. Consistent with the preclinical literature, this study suggests that naltrexone leads to earlier termination of drinking within a session.

In summary, the fine grained analyses of naltrexone's effects on drinking patterns within a session and across sessions suggest that there may be ways in which to better detect and maximize the efficacy of naltrexone. In the analysis of clinical trial data, greater attention should be given to patterns of drinking among those who lapse. Specific hypotheses regarding patterns of drinking could be tested using statistical approaches that take fuller advantage of the detailed drinking data collected, such as multiple time to event analyses (Andersen & Gill, 1982; Lawless & Nadeau, 1995). Clinically, the delay in time to drinking following a lapse provides a longer window for intervening with behavioral or motivational interventions; these interventions could be tailored

to take advantage of this effect of naltrexone. The data from preclinical and laboratory studies showing that the effects of naltrexone on drinking are more pronounced later in the session could be used to modify current protocols for reducing the risk of heavy drinking in nonalcohol-dependent problem drinkers. Specifically, these protocols might incorporate instructions to delay the time between drinks to allow greater opportunity for naltrexone-induced changes in the reinforcing effects of alcohol to become apparent. This advice might also be incorporated into the treatment of alcohol-dependent individuals following a lapse in abstinence that meets criteria for heavy drinking. Finally, evidence that naltrexone reduces drinking across sessions without requiring an initial deprivation from alcohol suggests that naltrexone therapy could be instituted prior to the establishment of abstinence, as was done successfully in the clinical trials of Heinala and colleagues (Heinala et al., 2001) and Morris and colleagues (Morris et al., 2001). In this case, several different models of treatment could be investigated. In the smoking cessation literature, for example, one model that has been used with bupropion involves starting the medication 1 week prior to the "quit date" on which the person attempts to quit smoking (Hurt et al., 1997). Whether naltrexone could be used in a similar way to reduce craving and drinking levels prior to a "quit date" could be subjected to empirical testing.

4. Dosing Regimens

4.1. Dose

The approved dose of naltrexone is 50 mg daily; this dose was chosen for treating alcoholism because it was used in treating opiate dependence to block the effects of exogenous opiates. It is not known whether this is the optimal dose for treating alcoholism. Many preclinical studies have demonstrated that the suppressive effects of naloxone and naltrexone on alcohol self-administration are dose-dependent (Froehlich et al., 1990; Holter & Spanagel, 1999; Hyttia & Sinclair, 1993; Schwarz-Stevens et al., 1992; Sharpe & Samson, 2001; Stromberg, Casale, Volpicelli, Volpicelli, & O'Brien, 1998a). The possibility that higher doses may be more effective in human subjects is suggested by the results of a dose ranging study by McCaul and colleagues in 109 alcohol-dependent patients, two-thirds of whom had comorbid other substance use disorders and who received 0,50, or 100 mg daily for 12 weeks (Litten & Fertig, 1996). The results showed that the 50 mg dose was better than placebo in the first month only; whereas the efficacy of 100 mg compared to placebo persisted up through the second month of treatment. In addition, a negative relationship was noted between **6-β-naltrexol** levels, an active metabolite of naltrexone, and drinking during the study. Paralleling this finding, a controlled human laboratory study by the same group found that 100 mg compared to 50 mg naltrexone resulted in lower ratings of liking for high dose alcohol and that higher

6- β -naltrexol levels were associated with this effect of naltrexone (McCaul et al., 2000). Given that a recent study has reported that 6- β -naltrexol is effective in suppressing alcohol consumption in a dose-dependent manner in rats, it is possible that individuals may also respond differently to naltrexone as a function of the **6- β -naltrexol** levels they attain (Rukstalis, Stromberg, O'Brien, & Volpicelli, 2000).

In the light of the limited dose ranging information available for naltrexone, many clinicians are taking a flexible approach to dosing, based on tolerability and efficacy. Dose-related hepatotoxicity, however, places an upper limit on the doses that can be used safely.

4.2. Continuous Release Formulations

Not surprisingly, it has been shown that compliance with naltrexone was an important determinant of treatment outcome in several studies. For example, the advantage of naltrexone over placebo is magnified in analyses restricted to the subset of patients who complied with medication and counseling sessions (Chick et al., 2000; Monti et al., 2001; Volpicelli et al., 1997). Given the central role of compliance, long-acting depot versions of naltrexone are under development to circumvent problems of noncompliance. In a preliminary study by Kranzler and colleagues (Kranzler et al., 1998), a continuous release injection of naltrexone administered to 15 subjects reduced the frequency of heavy drinking days during a 1-month injection period (when drug levels were sustained) and a 1-month follow-up period, compared to injection of a placebo given to five subjects. Additional research is examining the efficacy of this formulation administered to a larger sample for longer periods of time. An important advantage of these long-acting formulations is that they require less frequent administration (e.g., monthly) and so minimize the problems associated with noncompliance for this period. Depending on the release characteristics of long-acting formulations, it may also be possible to reduce adverse events related to high peak levels of drug associated with oral dosing and to reduce the overall level of drug exposure.

On the negative side, the preclinical literature suggests that tolerance to the suppressive effects of naltrexone on alcohol drinking may occur with continuous, sustained release of naltrexone. Though the vast majority of preclinical studies report that naloxone and naltrexone decrease alcohol drinking in a variety of experimental paradigms, a few preclinical reports indicate that naltrexone is not effective in all conditions due, in large part, to the development of tolerance to naltrexone during chronic administration of the drug. For instance, continuous administration of naltrexone via pellet implantation in rats (Iso & Brush, 1991) and mice (Phillips, Wenger, & Dorow, 1997) did not suppress alcohol intake but rather increased intake. Continuous administration of naloxone via osmotic minipump resulted in suppression of alcohol intake by rats during the beginning of the treatment period, but the suppression of drinking gradually disappeared during continuous naloxone administration

(Overstreet et al., 1999). Similarly, continuous administration of naltrexone via osmotic minipump in long-term alcohol experienced rats did not block the increase in alcohol intake seen following reexposure to alcohol in the alcohol deprivation model (ADE) of alcohol relapse (Holter & Spanagel, 1999), although naltrexone decreased alcohol intake, relative to saline treatment, on the first day of alcohol reexposure. Tolerance to naltrexone may occur because long-term (chronic) blockade of opioid receptors with an opioid receptor antagonist such as naltrexone can result in upregulation of opioid receptors and opioid receptor supersensitivity (Danks et al., 1988; Hytyia, Ingman, Soini, Laitinen, & Korpi, 1999; Morris, Millan, & Herz, 1988; Moudy, Spain, & Coscia, 1985; Rothman et al., 1989, 1990; Tempel, Gardner, & Zukin, 1985; Zukin et al., 1982). Notably, it has been shown that continuous administration of naloxone or naltrexone to rats via osmotic minipump results in a significant increase in opioid receptor concentrations in the brain and increased receptor concentration is paralleled by a decrease in the ability of naltrexone to reduce alcohol intake in a scheduled alcohol access paradigm (Overstreet et al., 1999) as well as in an alcohol deprivation model of alcohol relapse (Cowen, Rezvani, Jarrott, & Lawrence, 1999).

The failure of naltrexone to suppress alcohol intake when naltrexone is continuously administered has potential relevance for designing human naltrexone dosing regimens since the results of these studies suggest that continuous administration of naltrexone during abstinence may increase the reinforcing efficacy of alcohol upon redrinking. This, in turn, suggests that sustained or continuous release formulations of naltrexone may actually increase alcohol intake if and when relapse occurs. Designing a dosing regimen that will optimize the efficacy of naltrexone will require an evalution of various naltrexone doses and of timing naltrexone administration to identify a regimen that blocks endogenous opioid receptor populations without inducing opioid receptor supersensitivity. Currently, the conditions that induce opioid receptor supersensitivity in humans have not been fully characterized.

4.3. Long-Term Intermittent Naltrexone Administration

In current practice, naltrexone is administered daily or twice daily, not continuously. Continuous administration of naltrexone via sustained release formulations may induce tolerance to naltrexone and opioid receptor supersensitivity, but repeated administration of naltrexone, once a day or several times a day, would produce a pulsatile pattern of antagonist blockade at the receptor level which may avoid the development of tolerance and receptor supersensitivity. When designing clinical naltrexone treatment regimens, it is important to know whether tolerance to naltrexone will develop after long-term intermittent naltrexone administration (once or twice a day), and the preclinical data on this point are mixed. Some preclinical studies report a diminished ability of naltrexone to reduce alcohol intake ("naltrexone tolerance"), but during repeated naltrexone administration for many days (intermittently)

(Gardell et al., 1997; Myers & Lankford, 1996; Phillips et al., 1997), the majority of preclinical studies find that naloxone and naltrexone remain effective in reducing alcohol intake (Badia-Elder et al., 1999; Bienkowski et al., 1999; Froehlich, Harts, Lumeng, & Li, 1987; Gardell, Hubbell, & Reid, 1996; Overstreet et al., 1999; Parkes & Sinclair, 2000; Reid, Gardell, Chattopadhyay, & Hubbell, 1996b; Shelton & Grant, 2001; Stromberg et al., 2001; Stromberg, Volpicelli, & O'Brien, 1998b). The weight of the evidence from preclinical studies suggests that tolerance does not develop to chronic administration of naltrexone if low to moderate doses are used and administration is intermittent and timed to precede onset of alcohol access or introduction of alcohol-related cues. In fact, several preclinical studies on the long-term efficacy of naloxone and naltrexone indicate that the suppressive effects of naloxone (Hyytia & Sinclair, 1993; Sinclair, 1990) and naltrexone (Parkes & Sinclair, 2000; Stromberg, Volpicelli et al., 1998b) on alcohol intake actually increase over time with repeated intermittent antagonist treatment.

In human studies, there have been no reports of tolerance to the effects of naltrexone on alcohol drinking when naltrexone has been administered on a schedule of once a day or twice a day. Although the initial studies of naltrexone were 12 weeks in duration, naltrexone has been tested in trials lasting up to a year (Heinala et al., 2001; O'Malley, 1999; Rubio et al., 2001) and has been found effective. In the VA Naltrexone Cooperative Study (Krystal et al., 2001), there appeared to be an advantage of long-term naltrexone treatment for 1 year on median number of days to relapse to heavy drinking, compared to short-term naltrexone or placebo although this was not tested statistically.

4.4. Targeted Naltrexone

The preclinical literature suggests that prolonged clinical use of naltrexone, administered intermittently, should be useful in reducing alcohol drinking. However, tolerance to naltrexone during long-term intermittent treatment has been reported in a few studies which raises the possibility that there may be significant individual variations in the degree to which subjects develop tolerance to naltrexone and suggests that clinical treatment regimens should consider increasing naltrexone dosage during chronic treatment, when necessary, to ensure continued efficacy of the drug and/or inserting naltrexone-free periods in the naltrexone treatment regimen to allow for dissipation of tolerance, should it develop.

One approach to avoiding the development of tolerance to naltrexone is to omit naltrexone administration during abstinence and to administer the drug only on an "as needed" basis which might be signaled by the onset of alcohol craving (Heinala et al., 2001). This is not the same as administering naltrexone only during periods of alcohol drinking to induce "extinction" of the rewarding properties of alcohol (Hyytia & Sinclair, 1993; Sinclair, 1990). However, the efficacy of naltrexone depends on inducing an adequate opioid receptor blockade which takes a period of time to develop following onset of naltrexone

administration. Hence, naltrexone would have to be administered at the earliest stages of the onset of alcohol craving or prior to a predictable exposure to alcohol-related environmental cues. The inability of individuals to accurately predict where and when alcohol-related cues may be encountered could limit the utility of this approach. In one study, targeted use of naltrexone appeared to maintain the initial positive effect of naltrexone in patients treated with naltrexone daily for the first 12 weeks and who received concurrent coping skills therapy, followed by targeted naltrexone treatment during weeks 13–20 (Heinala et al., 2001). During the period of targeted naltrexone use, subjects self-administered on average 2.1 ± 0.02 pills per week. Thus, targeted use of naltrexone following an initial period of daily dosing also may provide a cost-effective approach to long-term treatment. Targeted use of naltrexone as an initial treatment approach for early problem drinkers has also been investigated in an open-label study with promising results (Kranzler, Tennen, Penta, & Bohn, 1997).

One potential dosing strategy that deserves investigation is combined use of daily dosing to cover unanticipated craving or encounters with drinking cues and an additional prn dose to be used prior to anticipated high-risk situations (e.g., a party) and in response to "breakthrough" urges to drink. This strategy might also help reduce the development of tolerance to the effects of naltrexone on craving and drinking by effectively alternating the dose of naltrexone administered. Similar approaches are being used with nicotine replacement products, in which combined use of transdermal nicotine patches provides steady-state nicotine replacement and nicotine gum is used as needed when craving is experienced (Kornitzer, Boutsen, Dramaix, Thijus, & Gustavsson, 1995).

4.5. Drinking Pattern Specific Dosing

Another variable to consider when determining the optimal use of naltrexone for decreasing alcohol intake is the pattern of alcohol drinking. Many of the preclinical studies in which naloxone or naltrexone decrease alcohol intake involve scheduled or limited access to alcohol, that is, the animal has access to alcohol, either orally consumed or operantly administered, for a limited period of time each day, and naloxone or naltrexone is administered prior to the alcohol access period. Clearly the efficacy of naltrexone depends on the presence of adequate concentrations of the antagonist at opioid receptor sites at the time of onset of alcohol drinking, reexposure to alcohol, or reexposure to alcohol-related cues that can induce alcohol craving or the urge to drink. The limited alcohol access paradigms used in many preclinical studies contain an element of moderate alcohol deprivation. However, even when rodents are given continuous access to alcohol throughout 24 hours, most of the alcohol consumption occurs in the dark portion of the light-dark cycle, and hence continuous access to alcohol also involves an element of moderate, "self-elected," daily deprivation. These preclinical conditions are analogous to

the discontinuous alcohol drinking patterns that are exhibited by most individuals with alcohol dependence where alcohol intake does not occur during sleep or during times of work and family demands. However, if alcohol drinking is continuous, it is conceivable that intermittent naltrexone treatment (e.g., once a day) may not be sufficient to reduce alcohol intake since metabolic clearance of the drug may result in inadequate levels of the antagonist at opioid receptor sites at the time of onset of alcohol drinking or onset of the urge to drink. Although speculative, this might suggest that in individuals who typically drink throughout the day, more frequent dosing of naltrexone might be useful while maintaining the intermittent characteristic of the treatment regimen (several doses spaced throughout the daily alcohol access interval).

5. Factors Predicting Clinical Response to Naltrexone

5.1. Genetic Response

Not all alcoholics respond to naltrexone with a decrease in alcohol drinking. This is due, in part, to the fact that individuals drink for different reasons that are influenced by both environmental and genetic factors. Hence, it would not be expected that one drug would serve the entire alcohol-dependent population equally well. A method is needed for predicting which subpopulations will respond to naltrexone and which would be better served by another type of medication or treatment approach. Currently, little is known about the genetic traits of individuals who respond to naltrexone versus those who do not. However, various lines of evidence suggest that individuals whose opioid systems are highly sensitive to alcohol may constitute a subpopulation for whom naltrexone is particularly effective in decreasing alcohol intake.

Recently, it has been estimated that genetic factors contribute at least 40% to the risk of alcoholism (Hesselbrock, 1995). The fact that genetic factors contribute to the development of alcoholism (Cadoret, Cain, & Grove, 1980; Cotton, 1979; Goodwin, 1985) has raised fundamental questions regarding the nature of what is inherited when one inherits a predisposition toward alcohol drinking. A genetic propensity toward high alcohol intake is determined undoubtedly by multiple genes that regulate a number of predisposing neurobiological factors. One of these factors appears to be increased sensitivity to the reinforcing effects of alcohol that may be mediated by alcohol-induced activation of the endogenous opioid system. Preclinical studies indicate that a genetic predisposition toward alcohol drinking is associated with increased sensitivity of the opioid system to alcohol in rodents (De Waele et al., 1992; Froehlich, 1995; Gianoulakis, 1998; Jamensky & Gianoulakis, 1997; Krishnan-Sarin et al., 1998; Li et al., 1998). Similar findings have been noted (Gianoulakis et al., 1989) and confirmed (Gianoulakis et al., 1996) in human populations at high risk (family history positive or FHP) or low risk (family history negative or FHN) for the future development of alcoholism, and the beta-endorphin response to

alcohol in humans, has been found to be highly heritable (Froehlich, Zink, Li, & Christian, 2000a). The fact that increased sensitivity of the opioid system to alcohol is associated with a genetic predisposition toward alcohol drinking in both rodents and humans suggests that opioid antagonists that block the action of endogenous opioid peptides may be more effective in decreasing alcohol drinking and relapse rates in an individual with a family history of alcoholism.

Consistent with this hypothesis, it has been shown that a family history of alcoholism predicts naltrexone response (Monterosso et al., 2001; O'Malley, 1999). In the Monterosso study (2001), familial loading for alcohol problems was computed as a percentage that reflected the proportion of the patient's relatives with alcohol problems, as reported on the Drug/Alcohol section of the ASI. First-degree relatives were weighted twice as heavily as second-degree relatives. The interaction between treatment condition and familial loading for alcohol problems was marginally significant; subjects who had higher familial loading showed the greatest naltrexone-induced reduction in the number of heavy drinking days, compared to placebo. A family history of alcoholism in first-degree relatives reportedly predicts continued benefit from naltrexone, compared to placebo, among those who responded to an initial 10-week treatment period with naltrexone (O'Malley, 1999).

5.2. *Craving*

The phenomenon of craving, alternatively termed urge or desire to drink, has been described as an emotional state that is characterized by the motivation to seek and use alcohol (Baker, Morse, & Sherman, 1987). Clinicians and researchers have been very interested in the potential role of the urge to drink as a predictor of relapse among abstinent alcoholics and as a potential target for pharmacotherapies (for reviews, see Meyer, 2000; Rohsenow & Monti, 1999). Although not entirely consistent, clinical trials (Anton et al., 1999; Chick et al., 2000; O'Malley et al., 1996) and human laboratory studies (Davidson et al., 1999; Monti et al., 1999; O'Malley et al., 2002) suggest that naltrexone treatment is associated with lower levels of the urge to drink, compared to placebo. These findings have led investigators to examine whether individuals with high levels of craving constitute a subgroup for whom naltrexone will be particularly helpful. The results support this view since craving for alcohol has been shown to be a significant predictor of medication response in three studies. Using data from the original 12-week Yale naltrexone study, Jaffe and colleagues (Jaffe et al., 1996) found that subjects with higher baseline levels of craving drank more per occasion on placebo compared to naltrexone. Similarly, Volpicelli and colleagues (Volpicelli et al., 1995) found that baseline craving interacted with naltrexone compared to placebo to predict the percentage of drinking days in their original naltrexone trial (Volpicelli et al., 1992). Finally, Monterosso et al. (2001) found that baseline craving, measured with the Penn Alcohol Craving Scale at the end of the placebo lead-in week, interacted with the medication condition to predict the number of days of heavy drinking

in the 12-week naltrexone trial. In all three studies, higher levels of baseline craving compared to lower levels of baseline craving were associated with heavier drinking during treatment with placebo, whereas drinking was low and comparable for subjects with low and high levels of baseline craving who received naltrexone. Thus, naltrexone appears to reverse the poor prognosis of high pretreatment levels of urge to drink.

5.3. Other Patient Characteristics

Other variables shown in single studies to predict of differential response to naltrexone are educational attainment, nonverbal learning, and somatic distress using the SCL-90 (Jaffe et al., 1996; Volpicelli et al., 1995). Variables that did not interact included number of years drinking, age, employment, marital status, and race (Volpicelli et al., 1995). In their meta-analysis of eight randomized naltrexone studies, Kranzler and Van Kirk (2001) found a trend for a greater effect of naltrexone in samples with higher baseline GGT levels and the Caucasian race. Predictor analyses using data from the VA Naltrexone Cooperative Study did not find any interactions between patient characteristics (i.e., psychiatric diagnoses, family history, motivation, craving, dependence, and age at onset of drinking) and medication condition in predicting response to treatment (Krystal et al., 2001). It has not been possible to examine gender as a predictor of response in these studies because they enrolled primarily men.

Observed interactions between patient characteristics and naltrexone response are dependent in part on the association between different levels of the patient characteristic and response to placebo. Specifically, in these studies the patient characteristic predicts drinking outcome in the placebo group. However, there is no difference in the drinking response of patients high and low on the prognostic variable in the naltrexone group. That is, the response of the poor prognosis group is comparable to that of the better prognosis patients when treated with naltrexone. Thus, these data suggest that patient characteristics that predict greater drinking may be useful in selecting patients for whom naltrexone may be particularly beneficial.

5.4. Interactions with Behavioral Interventions

Given that naltrexone reduces the frequency, amount, or timing of drinking among those who lapse, it follows that the therapeutic value of naltrexone may depend in part on the nature of the behavioral intervention and the likelihood that a lapse in abstinence may occur. Some of the strongest findings for naltrexone on relapse to heavy drinking, for example, have been in studies that used cognitive behavioral therapy (CBT) (Anton et al., 1999; Heinala et al., 2001; O'Malley et al., 1992); more modest effects are seen when supportive therapy is used (Heinala et al., 2001). As one component of CBT, patients are taught how to prevent a lapse from becoming a relapse, which may have the unintended

consequence of higher rates of lapses. In contrast, supportive therapies that emphasize abstinence may yield lower rates of lapses in abstinence and thus, might result in a reduced number of subjects for whom the effects of naltrexone on relapse drinking will be tested. For patients on placebo, any sampling of alcohol is likely to lead to heavy drinking, and even those who have been taught skills to cope with a lapse may not be able to interrupt this process. In contrast, naltrexone may reduce the ability of alcohol consumption to prime continued drinking and thereby make it possible for patients in CBT to use newly learned skills to interrupt drinking and resume abstinence. Patients receiving supportive therapy may not have the same cognitive and/or behavioral tools needed to build on the pharmacological effect of naltrexone. Perhaps this is one possible explanation for the negative findings of the VA Naltrexone Cooperative Study (Krystal et al., 2001). In this study, the behavioral treatments were strongly abstinence oriented and used 12-Step Facilitation Therapy, as well as feedback and counseling about medication compliance. Ultimately, relapse rates were low in the group who received placebo plus the behavioral treatment, which may have reduced the potential to test the effects of naltrexone on relapse. Similarly, the positive response to the treatment program alone in the Monti study (Monti et al., 2001) may have reduced the potential to test the effects of naltrexone in the intention to treat analysis. In this study, patients had successfully completed an intensive partial hospital program prior to introduction of the 3-month double blind medication phase. Ultimately, the added value of naltrexone may be most apparent in studies or clinical settings in which the behavioral platform is less intensive (e.g., a primary care model of counseling) or in populations that are likely to drink in spite of more intensive behavioral interventions (e.g., dual diagnosis patients, family history positive individuals, and those with high baseline craving).

5.5. Reduction of Heavy Drinking in Nonalcoholic Populations

The majority of naltrexone clinical trials have been conducted in alcohol-dependent patients. However, a large subgroup of people who drink heavily, but who do not meet alcohol dependence criteria, may also benefit from naltrexone therapy to help reduce heavy drinking rates. In a small pilot study, it was found that naltrexone in doses of 25 mg and 50 mg daily reduced heavy drinking during a six-week treatment period when combined with brief counseling in nondependent individuals (Bohn, Kranzler, Beazoglou, & Staehler, 1994). Using a similar population of heavy drinkers, Kranzler and colleagues (Kranzler et al., 1997) evaluated the feasibility of using naltrexone on an "as-needed" basis in anticipation of high-risk drinking sessions. In this paradigm, naltrexone significantly reduced a variety of drinking-related outcomes during the 6-week treatment period, and the effect of naltrexone persisted during a 3-month follow-up. In both of these studies, the subject was allowed to choose between a goal of abstinence or of drinking at "sensible" or nonhazardous levels.

Administering naltrexone on an "as needed" basis in clinical studies is analogous to administering naltrexone prior to an opportunity to drink in animal studies. Within this context, it is interesting to note that naloxone has been found to reduce the acquisition of alcohol drinking behavior in organisms with a genetic predisposition toward alcohol drinking if naloxone is administered concurrently with the first opportunity to drink alcohol (Badia-Elder et al., 1999). Repeated daily administration of moderate doses of naloxone retarded the acquisition of alcohol drinking in a dose-dependent manner in rats selectively bred for high alcohol drinking when naloxone treatment was initiated at the same time as introduction of alcohol availability. Although alcohol intake increased during 30 days of alcohol availability in rats who received daily naloxone treatment, overall daily alcohol intake in the naloxone-treated group was less than half of that seen in rats receiving a vehicle over the same time period. In mice, daily treatment with naltrexone retarded acquisition of alcohol drinking in an inbred strain known for high alcohol intake (C57BL/6J) but was ineffective in reducing alcohol intake in these mice after 5 days of alcohol drinking in the absence of naltrexone treatment (Phillips et al., 1997).

These preclinical findings in rodents may be of value in designing pharmacotherapeutic programs aimed at preventing the development of alcohol dependence. The results suggest that an effective early intervention strategy to prevent heavy alcohol drinking and subsequent alcohol dependence may be to use pharmacotherapeutic approaches to block the expression of a genetic predisposition toward alcohol drinking in individuals at genetic risk of developing alcoholism. The concept of using early intervention strategies to prevent the expression of diseases with a strong genetic component is not new. For instance, stimulation of hormonally active 1, 25-dihydroxyvitamin D3 is currently being explored as a therapeutic approach for preventing the expression of multiple sclerosis which is influenced by genetic traits (Hayes, Cantorna, & DeLuca, 1997). In addition, clinical studies are being conducted to test the efficacy of low-dose insulin and nicotinamide in preventing the expression of type 1 diabetes mellitus in individuals at genetic risk of developing this disease (Verge & Eisenbarth, 1996).

6. Combination Therapy

As previously stated, high alcohol intake is undoubtedly determined by multiple genes that regulate a number of predisposing neurobiological factors, and alcohol drinking is not mediated solely by the endogenous opioid system. A number of neurotransmitter/neuromodulator systems, including serotonin (5-HT) and glutamate, have been implicated in the control of alcohol drinking as well as in the postingestive effects of alcohol (Di Chiara et al., 1992; Koob et al., 1998; Weiss et al., 1992). Hence, it is not surprising that preclinical studies are investigating whether combining opioid receptor antagonists with agents that alter activity within the 5-HT and glutamate systems enhances

suppression of alcohol intake. It has been found that fluoxetine, a selective serotonin reuptake inhibitor (SSRI) widely prescribed for depression, decreases alcohol drinking in rodents (for a review, see Le et al., 1999) and, when combined with naloxone or naltrexone, is reportedly more effective than either agent alone in reducing alcohol intake (Rezvani et al., 2000; Zink, Rohrbach, & Froehlich, 1999), although increased efficacy is not always seen (Gardell et al., 1997). Preliminary clinical studies combining naltrexone and sertraline (Farren, Catapano, & O'Malley, 1997) and the 5-HT3 antagonist, ondansetron (Johnson, Ait-Daoud, & Prihoda, 2000), have shown promising results for drinking-related outcomes and are being followed up with larger randomized clinical trials. Additionally, a small open-label study evaluating the addition of naltrexone to depressed alcohol patients, who were stabilized on SSRIs (Salloum et al., 1998), found that combined treatment was associated with a reduction of the number of drinks consumed per week.

Preclinical studies using rodent models of alcohol craving and relapse, such as the ADE, indicate that both naltrexone and acamprosate (calcium acetyl homotaurinate) suppress the increase in alcohol drinking that often occurs following alcohol deprivation (Heyser, Schulteis, Durbin, & Koob, 1998; Holter, Landgraf, Zieglgansberger, & Spanagel, 1997; Spanagel et al., 1996) which suggests that naltrexone and acamprosate, when administered together, may be particularly effective for suppressing alcohol intake. Combining acamprosate with naltrexone, both of which have demonstrated clinical utility in reducing alcohol relapse, was reportedly more effective in suppressing alcohol intake than either drug alone in one rodent study (Froehlich, Zink, & Rohrbach, 2000b) but not in another (Stromberg et al., 2001). It is likely that the conflicting results for the preclinical effects of combining naltrexone with other agents is due to differences among studies in doses of the agents used as well as the experimental paradigms used to index alcohol self-administration. In humans, the safety of the naltrexone/acamprosate combination has been demonstrated in laboratory studies of normal volunteers (Mason, 1999) and alcohol-dependent subjects (Johnson, O'Malley, Ciraulo, Roache, Chambers, Sarid-Segal, & Couper, in press). A large scale NIAAA sponsored multisite study is underway to test the efficacy of these two medications alone and in combination when accompanied by behavioral interventions of different intensities. The results should provide comprehensive information about the clinical utility of this combined approach to treatment (O'Malley, Mattson, & The COMBINE Research Group, 2000).

7. Summary

Both preclinical and clinical studies are critical in the development of effective pharmacotherapeutic approaches for treating alcoholism. Nowhere has this been more evident than in the development of naltrexone for treating alcohol relapse. As studies continue on the use of naltrexone for modifying alcohol intake, promising avenues for continued work on maximizing the efficacy of

naltrexone for treating alcohol abuse and alcoholism are emerging. Recent research suggests that naltrexone can influence key components of alcohol dependence, including loss of control over the decision to drink and the amount of alcohol consumed. Although not uniformly positive, the majority of clinical trials supports the hypothesis that naltrexone can reduce the urge to drink, increase the number of days abstinent, and minimize the risk of relapse to heavy drinking. Human laboratory and preclinical paradigms that have investigated how naltrexone alters patterns of drinking suggest that naltrexone treatment results in earlier cessation of drinking within a session. In addition, preclinical data suggest that the amount of alcohol consumed declines during subsequent sessions in the presence of naltrexone. Based on this analysis, future clinical trials should consider using analytic approaches that evaluate patterns of drinking (e.g., multiple event analysis) rather than single events (e.g., survival analysis). Furthermore, behavioral interventions and instructions can also be developed to take advantage of this effect. Additional preclinical and clinical work is warranted to identify dosing strategies that ensure adequate drug levels while reducing the possibility of developing tolerance to naltrexone. Finally, studies designed to identify the characteristics of drinking populations that are responsive to naltrexone and studies investigating the potential advantage of combining naltrexone with agents that alter a number of neurotransmitter systems are exciting new avenues of research. Ultimately, these lines for research promise to provide critical information that can be used to maximize the efficacy of naltrexone for treating alcoholism.

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References

- Akil, H., Watson, S.J., Young, E., Lewis, M.E., Khachaturian, H., & Walker, J.M. (1984). Endogenous opioids: biology and function. *Annual Review of Neuroscience* 7, 223–255.
- Altshuler, H.L., Phillips, P.E., & Feinhandler, D.A. (1980). Alteration of ethanol self-administration by naltrexone. *Life Sciences* 26(9), 679–688.
- Andersen, P.K., & Gill, R.D. (1982). Cox's regression model for counting processes: a large sample study. *Annals of Statistics* 10, 1100–1120.
- Anton, R.F., Moak, D.H., Waid, L.R., Latham, P.K., Malcolm, R.J., & Dias, J.K. (1999). Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *American Journal of Psychiatry* 156(11), 1758–1764.
- Anton, R., Moak, D.H., Latham, P.K., Waid, L.R., Malcolm, R.J., Dias, J.K., & Roberts, J.S. (2001). Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *Journal of Clinical Psychopharmacology* 21(1), 72–77.
- Badia-Elder, N.E., Mosemiller, A.K., Elder, R.L., & Froehlich, J.C. (1999). Naloxone retards the expression of a genetic predisposition toward alcohol drinking. *Psychopharmacology (Berl)* 144(3), 205–212.
- Baker, T.B., Morse, E., & Sherman, J.E. (1987). *The Motivation to Use Drugs: A Psychobiological Analysis of Urges*. Lincoln, NE: University of Nebraska Press.

- Benjamin, D., Grant, E.R., & Pohorecky, L.A. (1993). Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. *Brain Research* 621(1), 137–140.
- Bienkowski, P., Kostowski, W., & Koros, E. (1999). Ethanol-reinforced behavior in the rat: Effects of naltrexone. *European Journal of Pharmacology* 374(3), 321–327.
- Bohn, M.J., Kranzler, H.R., Beazoglou, D., & Staehler, B.A. (1994). Naltrexone and brief counseling to reduce heavy drinking. *American Journal on Addictions* 2, 91–99.
- Brown, S.A., Vik, P.W., Patterson, T.L., Grant, I., & Schuckit, M.A. (1995). Stress, vulnerability and adult alcohol relapse. *Journal of Studies on Alcohol* 56(5), 538–545.
- Cadoret, R.J., Cain, C.A., & Grove, W.M. (1980). Development of alcoholism in adoptees raised apart from alcoholic biologic relatives. *Archives of General Psychiatry* 37(5), 561–563.
- Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, D.C., Farmer, R., Labriola, D., Marshall, J., Moncrieff, J., Morgan, M.Y., Peters, T., & Ritson, B. (2000). A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol and Alcoholism* 35(6), 587–593.
- Cotton, N.S. (1979). The familial incidence of alcoholism. *Journal of Studies on Alcohol* 40, 89–116.
- Cowen, M.S., Rezvani, A.H., Jarrott, B., & Lawrence, A.J. (1999). Ethanol consumption by Fawn-Hooded rats following abstinence: Effect of naltrexone and changes in mu-opioid receptor density. *Alcoholism: Clinical and Experimental Research* 23(6), 1008–1014.
- Danks, J.A., Tortella, F.C., Long, J.B., Bykov, V., Jacobson, A.E., Rice, K.C., Holaday, J.W., & Rothman, R.B. (1988). Chronic administration of morphine and naltrexone upregulate [³H]D-Ala₂-D-leu₅]enkephalin binding sites by different mechanisms. *Neuropharmacology* 27(9), 965–974.
- Davidson, D., Swift, R., & Fitz, E. (1996). Naltrexone increases the latency to drink alcohol in social drinkers. *Alcoholism: Clinical and Experimental Research* 20(4), 732–739.
- Davidson, D., Palfai, T., Bird, C., & Swift, R. (1999). Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcoholism: Clinical and Experimental Research* 23(2), 195–203.
- De Waele, J.P., Papachristou, D.N., & Gianoulakis, C. (1992). The alcohol-preferring C57BL/6 mice present an enhanced sensitivity of the hypothalamic beta-endorphin system to ethanol than the alcohol-avoiding DBA/2 mice. *Journal of Pharmacology & Experimental Therapeutics* 261(2), 788–794.
- Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America* 85(14), 5274–5278.
- Di Chiara, G., Acquas, E., & Carboni, E. (1992). Drug motivation and abuse: A neurobiological perspective. *Annals of the New York Academy of Sciences* 654, 207–219.
- Farren, C.K., Catapano, D., & O'Malley, S. (1997). Sertraline with naltrexone vs naltrexone alone in the treatment of alcohol dependence. *Alcoholism: Clinical and Experimental Research* 21(suppl), 64A.
- Froehlich, J.C. (1995). Genetic factors in alcohol self-administration. *Journal of Clinical Psychiatry* 56 (Suppl 7), 15–23.
- Froehlich, J.C. (1997). Physiology of opioid peptides. *Alcohol Health and Research World* 21, 132–136.
- Froehlich, J.C., & Li, T.K. (1993). Recent developments in alcoholism: Opioid peptides. *Recent Developments in Alcoholism* 11, 187–205.
- Froehlich, J.C., & Li, T.K. (1994). Opioid involvement in alcohol drinking. *Annals of the New York Academy of Sciences* 739, 156–167.
- Froehlich, J.C., Harts, J., Lumeng, L., & Li, T.K. (1987). Naloxone attenuation of voluntary alcohol consumption. *Alcohol and Alcoholism Suppl 1*, 333–337.
- Froehlich, J.C., Harts, J., Lumeng, L., & Li, T.K. (1990). Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. *Pharmacology, Biochemistry and Behavior* 35(2), 385–390.
- Froehlich, J.C., Zweifel, M., Harts, J., Lumeng, L., & Li, T.K. (1991). Importance of delta opioid receptors in maintaining high alcohol drinking. *Psychopharmacology* 103(4), 467–472.
- Froehlich, J.C., Zink, R.W., Li, T.K., & Christian, J.C. (2000a). Analysis of heritability of hormonal responses to alcohol in twins: Beta-endorphin as a potential biomarker of genetic risk for alcoholism. *Alcoholism: Clinical and Experimental Research* 24(3), 265–277.

- Froehlich, J.C., Zink, R.W., & Rohrbach, K. (2000b). Preclinical medications development: Combining naltrexone with acamprosate produces enhanced suppression of alcohol drinking in alcohol-preferring (P) rats. *Alcoholism: Clinical and Experimental Research* 24, 78A.
- Gardell, L.R., Hubbell, C.L., & Reid, L.D. (1996). Naltrexone persistently reduces rats' intake of a palatable alcoholic beverage. *Alcoholism: Clinical and Experimental Research* 20(3), 584–588.
- Gardell, L.R., Whalen, C.A., Chattophadyay, S., Cavallaro, C.A., Hubbell, C.L., & Reid, L.D. (1997). Combination of naltrexone and fluoxetine on rats' propensity to take alcoholic beverage. *Alcoholism: Clinical and Experimental Research* 21(8), 1435–1439.
- Gianoulakis, C. (1990). Characterization of the effects of acute ethanol administration on the release of beta-endorphin peptides by the rat hypothalamus. *European Journal of Pharmacology* 180(1), 21–29.
- Gianoulakis, C. (1998). Alcohol seeking behavior: The roles of the hypothalamic–pituitary–adrenal axis and the endogenous opioid system. *Alcohol Health and Research World* 22, 202–210.
- Gianoulakis, C., Hutchison, W.D., & Kalant, H. (1988). Effects of ethanol treatment and withdrawal on biosynthesis and processing of proopiomelanocortin by the rat neurointermediate lobe. *Endocrinology* 122(3), 817–825.
- Gianoulakis, C., Beliveau, D., Angelogianni, P., Meaney, M., Thavundayil, J., Tawar, V., & Dumas, M. (1989). Different pituitary beta-endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. *Life Sciences* 45(12), 1097–1109.
- Gianoulakis, C., De Waele, J.P., & Thavundayil, J. (1996). Implication of the endogenous opioid system in excessive ethanol consumption. *Alcohol* 13(1), 19–23.
- Gonzales, R.A., & Weiss, F. (1998). Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *Journal of Neuroscience* 18(24), 10663–10671.
- Goodwin, D.W. (1985). Alcoholism and genetics. The sins of the fathers. *Archives of General Psychiatry* 42(2), 171–174.
- Hayes, C.E., Cantorna, M.T., & DeLuca, H.F. (1997). Vitamin D and multiple sclerosis. *Proceedings of the Society for Experimental Biology and Medicine* 216(1), 21–27.
- Heinala, P., Alho, H., Kiiasmaa, K., Lonnqvist, J., & Kuoppasalmi, K. (2001). Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind, placebo-controlled trial. *Journal of Clinical Psychopharmacology* 21(3), 287–292.
- Henry, J.L. (1982). Circulating opioids: Possible physiological roles in central nervous function. *Neuroscience and Biobehavioral Reviews* 6(3), 229–245.
- Hersh, D., Van Kirk, J.R., & Kranzler, H.R. (1998). Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology (Berl)* 139(1–2), 44–52.
- Herz, A. (1997). Endogenous opioid systems and alcohol addiction. *Psychopharmacology (Berl)* 129(2), 99–111.
- Hesselbrock, V.M. (1995). The genetic epidemiology of alcoholism. In H. Begleiter & B. Kissin (eds.), *The Genetics of Alcoholism*. New York: Oxford University Press, pp. 17–39.
- Heyser, C.J., Schulteis, G., & Koob, G.F. (1997). Increased ethanol self-administration after a period of imposed ethanol deprivation in rats trained in a limited access paradigm. *Alcoholism: Clinical and Experimental Research* 21(5), 784–791.
- Heyser, C.J., Schulteis, G., Durbin, P., & Koob, G.F. (1998). Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. *Neuropsychopharmacology* 18(2), 125–133.
- Heyser, C.J., Roberts, A.J., Schulteis, G., & Koob, G.F. (1999). Central administration of an opiate antagonist decreases oral ethanol self-administration in rats. *Alcoholism: Clinical and Experimental Research*, 23(9) 1468–1476.
- Holter, S.M., & Spanagel, R. (1999). Effects of opiate antagonist treatment on the alcohol deprivation effect in long-term ethanol-experienced rats. *Psychopharmacology (Berl)* 145(4), 360–369.
- Holter, S.M., Landgraf, R., Zieglgansberger, W., & Spanagel, R. (1997). Time course of acamprosate action on operant ethanol self-administration after ethanol deprivation. *Alcoholism: Clinical and Experimental Research* 21(5), 862–868.
- Hore, B.D. (1971). Factors in alcoholic relapse. *British Journal of Addiction to Alcohol and Other Drugs* 66(2), 89–96.

- Hubbell, C.L., & Reid, L. (1990). Opioids modulate rats' intakes of alcoholic beverages. In L. Reid (ed.), *Opioids, Bulimia, and Alcohol Abuse and Alcoholism*. New York: Springer-Verlag.
- Hubbell, C.L., Czirr, S.A., Hunter, G.A., Beaman, C.M., LeCann, N.C., & Reid, L.D. (1986). Consumption of ethanol solution is potentiated by morphine and attenuated by naloxone persistently across repeated daily administrations. *Alcohol* 3(1), 39–54.
- Hubbell, C.L., Marglin, S.H., Spitalnic, S.J., Abelson, M.L., Wild, K.D., & Reid, L.D. (1991). Opioidergic, serotonergic, and dopaminergic manipulations and rats' intake of a sweetened alcoholic beverage. *Alcohol* 8(5), 355–367.
- Hurt, R.D., Sachs, D., Glover, E.D., Offord, K.P., Johnston, J.A., Dale, L.C., Khayrallah, M.A., Schroeder, D.R., Glover, P.N., Sullivan, C.R., Croghan, I.T., & Sullivan, P.M. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *The New England Journal of Medicine* 337(17), 1195–1202.
- Hytyia, P., & Kianmaa, K. (2001). Suppression of ethanol responding by centrally administered CTOP and naltrindole in AA and Wistar rats. *Alcoholism: Clinical and Experimental Research* 25(1), 25–33.
- Hytyia, P., & Sinclair, J.D. (1993). Responding for oral ethanol after naloxone treatment by alcohol-prefering AA rats. *Alcoholism: Clinical and Experimental Research* 17(3), 631–636.
- Hytyia, P., Ingman, K., Soini, S.L., Laitinen, J.T., & Korpi, E.R. (1999). Effects of continuous opioid receptor blockade on alcohol intake and up-regulation of opioid receptor subtype signalling in a genetic model of high alcohol drinking. *Naunyn Schmiedebergs Archives of Pharmacology* 360, 391–401.
- Iso, H., & Brush, F.R. (1991). Opposite effects of naltrexone on ETOH intake by Syracuse high and low avoidance rats. *Alcohol* 8(6), 443–448.
- Jaffe, A.J., Rounsville, B., Chang, G., Schottenfeld, R.S., Meyer, R.E., & O'Malley, S.S. (1996). Naltrexone, relapse prevention, and supportive therapy with alcoholics: An analysis of patient treatment matching. *Journal of Consulting and Clinical Psychology* 64(5), 1044–1053.
- Jamensky, N.T., & Gianoulakis, C. (1997). Content of dynorphins and kappa-opioid receptors in distinct brain regions of C57BL/6 and DBA/2 mice. *Alcoholism: Clinical and Experimental Research* 21(8), 1455–1464.
- Janal, M.N., Colt, E.W., Clark, W.C., & Glusman, M. (1984). Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: Effects of naloxone. *Pain* 19(1), 13–25.
- Johnson, B.A., Ait-Daoud, N., & Prihoda, T.J. (2000). Combining ondansetron and naltrexone effectively treats biologically predisposed alcoholics: From hypotheses to preliminary clinical evidence. *Alcoholism: Clinical and Experimental Research* 24(5), 737–742.
- Johnson, B.A., O'Malley, S., Ciraulo, D.A., Roache, J.D., Chambers, R.A., Sarid-Segal, O., & Couper, D. (in press). Dose-ranging kinetics and safety assessment of naltrexone and acamprosate both alone and combined in alcohol-dependent subjects. *Journal of Clinical Psychopharmacology*.
- Katner, S.N., & Weiss, B. (1999). Ethanol-associated olfactory stimuli reinstate ethanol-seeking behavior after extinction and modify extracellular dopamine levels in the nucleus accumbens. *Alcoholism: Clinical and Experimental Research* 23(11), 1751–1760.
- Katner, S.N., Kerr, T.M., & Weiss, F. (1996). Ethanol anticipation enhances dopamine efflux in the nucleus accumbens of alcohol-prefering (P) but not Wistar rats. *Behavioral Pharmacology* 7, 669–674.
- King, A.C., Volpicelli, J.R., Frazer, A., & O'Brien, C.P. (1997). Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. *Psychopharmacology (Berl)* 129(1), 15–22.
- Koob, G.F. (1992). Neural mechanisms of drug reinforcement. *Annals of the New York Academy of Sciences* 654, 171–191.
- Koob, G.F., & Bloom, F.E. (1983). Behavioural effects of opioid peptides. *British Medical Bulletin* 39(1), 89–94.
- Koob, G.F., Roberts, A.J., Schulteis, G., Parsons, L.H., Heyser, C.J., Hytyia, P., Merlo-Pich, E., & Weiss, F. (1998). Neurocircuitry targets in ethanol reward and dependence. *Alcoholism: Clinical and Experimental Research* 22(1), 3–9.

- Kornet, M., Goosen, C., & Van Ree, J.M. (1991). Effect of naltrexone on alcohol consumption during chronic alcohol drinking and after a period of imposed abstinence in free-choice drinking rhesus monkeys. *Psychopharmacology* 104(3), 367–376.
- Kornitzer, M., Boutsen, M., Dramaix, M., Thijus, J., & Gustavsson, G. (1995). Combined use of nicotine patch and gum in smoking cessation—a placebo-controlled clinical-trial. *Preventive Medicine* 24(1), 41–47.
- Kranzler, H., & Van Kirk, J. (2001). Efficacy of naltrexone and acamprosate for alcoholism treatment: A meta-analysis. *Alcoholism: Clinical and Experimental Research* 25(9), 1334–1341.
- Kranzler, H.R., Tennen, H., Penta, C., & Bohn, M.J. (1997). Targeted naltrexone treatment of early problem drinkers. *Addictive Behaviors* 22(3), 431–436.
- Kranzler, H.R., Modesto-Lowe, V., & Nuwayser, E.S. (1998). Sustained-release naltrexone for alcoholism treatment: A preliminary study. *Alcoholism: Clinical and Experimental Research* 22(5), 1074–1079.
- Kranzler, H.R., Modesto-Lowe, V., Van Kirk, J., & J. D. (2000). Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial. *Neuropsychopharmacology* 22(5), 493–503.
- Krishnan-Sarin, S., Jing, S.L., Kurtz, D.L., Zweifel, M., Portoghese, P.S., Li, T.K., & Froehlich, J.C. (1995a). The delta opioid receptor antagonist naltrindole attenuates both alcohol and saccharin intake in rats selectively bred for alcohol preference. *Psychopharmacology (Berl)* 120(2), 177–185.
- Krishnan-Sarin, S., Portoghese, P.S., Li, T.K., & Froehlich, J.C. (1995b). The delta 2-opioid receptor antagonist nalmefene selectively attenuates alcohol intake in rats bred for alcohol preference. *Pharmacology, Biochemistry and Behavior* 52(1), 153–159.
- Krishnan-Sarin, S., Wand, G.S., Li, X.W., Portoghese, P.S., & Froehlich, J.C. (1998). Effect of mu opioid receptor blockade on alcohol intake in rats bred for high alcohol drinking. *Pharmacology, Biochemistry and Behavior* 59(3), 627–635.
- Krystal, J.H., Cramer, J.A., Krol, W.F., Kirk, G.F., Rosenheck, R., & Veterans Affairs Naltrexone Cooperative Study 425 Group. (2001). Naltrexone in the treatment of alcohol dependence. *New England Journal of Medicine* 345, 1734–1739.
- Lawless, J.F., & Nadeau, J.C. (1995). Some simple robust methods for the analysis of recurrent events. *Technometrics* 37,158–168.
- Le, A.D., Poulos, C.X., Quan, B., & Chow, S. (1993). The effects of selective blockade of delta and mu opiate receptors on ethanol consumption by C57BL/6 mice in a restricted access paradigm. *Brain Research* 630(1–2), 330–332.
- Le, A.D., Poulos, C.X., Harding, S., Watchus, J., Juzytsch, W., & Shaham, Y. (1999). Effects of naltrexone and fluoxetine on alcohol self-administration and reinstatement of alcohol seeking induced by priming injections of alcohol and exposure to stress. *Neuropsychopharmacology* 21, 435–444.
- Li, X.W., Li, T.K., & Froehlich, J.C. (1998). Enhanced sensitivity of the nucleus accumbens proenkephalin system to alcohol in rats selectively bred for alcohol preference. *Brain Research* 794(1), 35–47.
- Litten, R.Z., & Fertig, J. (1996). International update: New findings on promising medications. *Alcoholism: Clinical and Experimental Research* 20(8 Suppl), 216A–218A.
- Ludwig, A.M., Wikler, A., & Stark, L.H. (1974). The first drink: Psychobiological aspects of craving. *Archives of General Psychiatry* 30(4), 539–547.
- Mason, B. (1999). Cognitive effects of naltrexone and acamprosate administered alone and in combination. Paper presented at the *Scientific Meeting of the Research Society on Alcoholism*, Santa Barbara, CA.
- McCaull, M.E., Wand, G.S., Eissenberg, T., Rohde, C.A., & Cheskin, L.J. (2000). Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. *Neuropsychopharmacology* 22(5), 480–492.
- McCullough, D.E., Mosemiller, A.K., Zhou, F.C., Portoghese, P.S., & Froehlich, J.C. (1998). Infusion of a delta opioid antagonist into the ventral tegmental area attenuates alcohol drinking in P rats. *Alcoholism: Clinical and Experimental Research* 22, 47A.
- McCullough, D., Mosemiller, A.K., Portoghese, P.S., & Froehlich, J.C. (1999). Infusion of a delta opioid receptor antagonist into the VTA produces early termination of alcohol drinking in P rats given scheduled access to alcohol. *Alcoholism: Clinical and Experimental Research* 23, 16A.

- McCullough, D., Portoghese, P.S., & Froehlich, J.C. (2000). Infusion of a delta opioid receptor antagonist into the nucleus accumbens reduces alcohol intake in alcohol preferring (P) rats. *Alcoholism: Clinical and Experimental Research* 24, 83A.
- McKinzie, D.L., Nowak, K.L., Yorger, L., McBride, W.J., Murphy, J.M., Lumeng, L., & Li, T.K. (1998). The alcohol deprivation effect in the alcohol-preferring P rat under free-drinking and operant access conditions. *Alcoholism: Clinical and Experimental Research*, 22(5) 1170–1176.
- Meyer, R.E. (2000). Craving: What can be done to bring the insights of neuroscience, behavioral science and clinical science into synchrony. *Addiction* 95 Suppl 2, S219–227.
- Monterosso, J.R., Flannery, B.A., Pettinati, H.M., Oslin, D.W., Rukstalis, M., O'Brien, C.P., & Volpicelli, J.R. (2001). Predicting treatment response to naltrexone: The influence of craving and family history. *American Journal on Addictions* 10, 258–268.
- Monti, P.M., Rohsenow, D.J., Rubonis, A.V., Niaura, R.S., Sirota, A.D., Colby, S.M., & Abrams, D.B. (1993). Alcohol cue reactivity: Effects of detoxification and extended exposure. *Journal of Studies on Alcohol* 54(2), 235–245.
- Monti, P.M., Rohsenow, D.J., Hutchison, K.E., Swift, R.M., Mueller, T.I., Colby, S.M., Brown, R.A., Gulliver, S.B., Gordon, A., & Abrams, D.B. (1999). Naltrexone's effect on cue-elicited craving among alcoholics in treatment. *Alcoholism: Clinical and Experimental Research* 23(8), 1386–1394.
- Monti, P.M., Rohsenow, D.J., Swift, R., Gulliver, S.B., Colby, S.M., Mueller, T.I., Brown, R.A., Gordon, A., Abrams, D.B., Niaura, R.S., & Asher, M.K. (2001). Naltrexone and cue exposure with coping and communication skills training for alcoholics: Treatment process and 1-year outcomes. *Alcoholism: Clinical and Experimental Research* 25, 1634–1647.
- Morris, B.J., Millan, M.J., & Herz, A. (1988). Antagonist-induced opioid receptor upregulation. II. Regionally specific modulation of mu, delta and kappa binding sites in rat brain revealed by quantitative autoradiography. *Journal of Pharmacology and Experimental Therapeutics* 247(2), 729–736.
- Morris, P.L.P., Hopwood, M., Whelan, G., Gardiner, J., & Drummond, E. (2001). Naltrexone for alcohol dependence: A randomized controlled trial. *Addiction* 96
- Moudy, A.M., Spain, J.W., & Coscia, C.J. (1985). Differential up-regulation of microsomal and synaptic membrane mu opioid receptors. *Biochemical and Biophysical Research Communications* 132(2), 735–741.
- Myers, R.D., & Lankford, M.F. (1996). Suppression of alcohol preference in high alcohol drinking rats: efficacy of amperozide versus naltrexone. *Neuropsychopharmacology* 14(2), 139–149.
- O'Malley, S.S. Naltrexone therapy: Predictors of adverse events, medication compliance and clinical treatment outcome. Symposium: Naltrexone treatment of alcoholism: Recent evidence from clinical research. Paper presented at the *Research Society on Alcoholism Scientific Meeting*, Santa Barbara, CA, July 1, 1999.
- O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Archives of General Psychiatry* 49(11), 881–887.
- O'Malley, S.S., Jaffe, A.J., Rode, S., & Rounsaville, B.J. (1996). Experience of a "slip" among alcoholics treated with naltrexone or placebo. *American Journal of Psychiatry* 153(2), 281–283.
- O'Malley, S.S., Mattson, M.E., & The COMBINE Research Group. Design and rationale for COMBINE, a multi-study on combining medications and behavior interventions for alcohol dependence. Paper presented at the *Research Society on Alcoholism Scientific Meeting*, Denver, CO, June 25, 2000.
- O'Malley, S.S., Krishnan-Sarin, S., Farren, C., Sinha, R., & Kreek, M.J. (2002). Naltrexone decreases craving and alcohol self-administration in alcohol dependent subjects and activates the hypothalamic–pituitary–adrenocortical axis. *Psychopharmacology* 160, 19–29.
- Overstreet, D.H., Kampov-Polevoy, A.B., Rezvani, A.H., Braun, C., Bartus, R.T., & Crews, F.T. (1999). Suppression of alcohol intake by chronic naloxone treatment in P rats: Tolerance development and elevation of opiate receptor binding. *Alcoholism: Clinical and Experimental Research* 23(11), 1761–1771.
- Parkes, H., & Sinclair, J.D. (2000). Reduction of alcohol drinking and upregulation of opioid receptors by oral naltrexone in AA rats. *Alcohol* 21(3), 215–221.

- Phillips, T.J., Wenger, C.D., & Dorow, J.D. (1997). Naltrexone effects on ethanol drinking acquisition and on established ethanol consumption in C57BL/6J mice. *Alcoholism: Clinical and Experimental Research* 21(4), 691–702.
- Reid, L.D. (1996a). Endogenous opioids and alcohol dependence: Opioid alkaloids and the propensity to drink alcoholic beverages. *Alcohol* 13(1), 5–11.
- Reid, L.D., Gardell, L.R., Chattopadhyay, S., & Hubbell, C.L. (1996b). Periodic naltrexone and propensity to take alcoholic beverage. *Alcoholism: Clinical and Experimental Research* 20(8), 1329–1334.
- Rezvani, A.H., Overstreet, D.H., Mason, G.A., Janowsky, D.S., Hamed, M., Clark, E., Jr., & Yang, Y. (2000). Combination pharmacotherapy: A mixture of small doses of naltrexone, fluoxetine, and a thyrotropin-releasing hormone analogue reduces alcohol intake in three strains of alcohol-preferring rats. *Alcohol and Alcoholism* 35(1), 76–83.
- Rodd-Henricks, Z.A., McKinzie, D.L., Murphy, J.M., McBride, W.J., Lumeng, L., & Li, T.K. (2000). The expression of an alcohol deprivation effect in the high-alcohol-drinking replicate rat lines is dependent on repeated deprivations. *Alcoholism: Clinical and Experimental Research* 24(6), 747–753.
- Rohsenow, D.J., & Monti, J. (1999). Does urge to drink predict relapse after treatment? *Alcohol Research and Health* 23, 225–232.
- Rothman, R.B., Bykov, V., Long, J.B., Brady, L.S., Jacobson, A.E., Rice, K.C., & Holaday, J.W. (1989). Chronic administration of morphine and naltrexone up-regulate mu-opioid binding sites labeled by [³H][D-Ala₂,MePhe₄,Gly-ol₅]enkephalin: Further evidence for two mu-binding sites. *European Journal of Pharmacology* 160(1), 71–82.
- Rothman, R.B., Long, J.B., Bykov, V., Jacobson, A.E., Rice, K.C., & Holaday, J.W. (1990). Pretreatment of rats with the irreversible mu-receptor antagonist, beta-FNA, fails to prevent naltrexone-induced upregulation of mu-opioid receptors. *Neuropharmacology* 29(9), 805–810.
- Rubio, G., Jimenez-Arriero, M.A., Ponce, G., & Palomo, T. (2001). Naltrexone versus acamprosate: One year follow-up of alcohol dependence treatment. *Alcohol and Alcoholism* 36(5), 419–425.
- Rukstalis, M.R., Stromberg, M.F., O'Brien, C.P., & Volpicelli, J.R. (2000). 6-beta-Naltrexol reduces alcohol consumption in rats. *Alcoholism: Clinical and Experimental Research* 24(10), 1593–1596.
- Salloum, I.M., Cornelius, J.R., Thase, M.E., Daley, D.C., Kirisci, L., & Spotts, C. (1998). Naltrexone utility in depressed alcoholics. *Psychopharmacol Bulletin* 34(1), 111–115.
- Schwarz-Stevens, K.S., Files, F.J., & Samson, H.H. (1992). Effects of morphine and naloxone on ethanol- and sucrose-reinforced responding in nondeprived rats. *Alcoholism: Clinical and Experimental Research* 16(4), 822–832.
- Seizinger, B.R., Bovermann, K., Maysinger, D., Hollt, V., & Herz, A. (1983). Differential effects of acute and chronic ethanol treatment on particular opioid peptide systems in discrete regions of rat brain and pituitary. *Pharmacology, Biochemistry and Behavior* 18 Suppl 1, 361–369.
- Sharpe, A.L., & Samson, H.H. (2001). Effect of naloxone on appetitive and consummatory phases of ethanol self-administration. *Alcoholism: Clinical and Experimental Research* 25(7), 1006–1011.
- Shelton, K.L., & Grant, K.A. (2001). Effects of naltrexone and Ro 15-4513 on a multiple schedule of ethanol and Tang self-administration. *Alcoholism: Clinical and Experimental Research* 25, 1576–1585.
- Sinclair, J.D. (1990). Drugs to decrease alcohol drinking. *Annals of Medicine* 22(5), 357–362.
- Sinclair, J.D., & Senter, R.J. (1967). Increased preference for ethanol in rats following alcohol deprivation. *Psychonomic Science* 8, 11–12.
- Sinclair, J.D., Walker, S., & Jordan, W. (1973). Behavioral and physiological changes associated with various durations of alcohol deprivation in rats. *Quarterly Journal of Studies on Alcohol* 34(3), 744–757.
- Siviy, S.M., Calcagnetti, D.J., & Reid, L.D. (1982). A temporal analysis of naloxone's suppressant effect on drinking. *Pharmacology, Biochemistry and Behavior* 16(1), 173–175.
- Spanagel, R., & Holter, S.M. (2000). Pharmacological validation of a new animal model of alcoholism. *Journal of Neural Transmission (Budapest)* 107(6), 669–680.
- Spanagel, R., Holter, S.M., Allingham, K., Landgraf, R., & Zieglgansberger, W. (1996). Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. *Eur J Pharmacol*, 305(1–3), 39–44.

- Staiger, P.K., & White, J.M. (1991). Cue reactivity in alcohol abusers: Stimulus specificity and extinction of the responses. *Addictive Behaviors* 16(5), 211–221.
- Stewart, J., & de Wit, H. (1987). Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In M.A. Bozarth (ed.), *Methods of Assessing the Reinforcing Properties of Abused Drugs*. New York: Springer-Verlag, pp. 211–227.
- Streeton, C., & Whelan, G. (2001). Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized clinical trials. *Alcohol and Alcoholism* 36(6), 544–552.
- Stromberg, M.F., Casale, M., Volpicelli, L., Volpicelli, J.R., & O'Brien, C.P. (1998a). A comparison of the effects of the opioid antagonists naltrexone, naltrindole, and beta-funaltrexamine on ethanol consumption in the rat. *Alcohol* 15(4), 281–289.
- Stromberg, M.F., Volpicelli, J.R., & O'Brien, C.P. (1998b). Effects of naltrexone administered repeatedly across 30 or 60 days on ethanol consumption using a limited access procedure in the rat. *Alcoholism: Clinical and Experimental Research* 22(9), 2186–2191.
- Stromberg, M.F., Mackler, S.A., Volpicelli, J.R., & O'Brien, C.P. (2001). Effect of acamprosate and naltrexone, alone or in combination, on ethanol consumption. *Alcohol* 23(2), 109–116.
- Swift, R.M., Whelihan, W., Kuznetsov, O., Buongiorno, G., & Hsuing, H. (1994). Naltrexone-induced alterations in human ethanol intoxication. *American Journal of Psychiatry* 151(10), 1463–1467.
- Tempel, A., Gardner, E.L., & Zukin, R.S. (1985). Neurochemical and functional correlates of naltrexone-induced opiate receptor up-regulation. *Journal of Pharmacology and Experimental Therapeutics* 232(2), 439–444.
- Verge, C.F., & Eisenbarth, G.S. (1996). Strategies for preventing type I diabetes mellitus. [see comments]. *Western Journal of Medicine* 164(3), 249–255.
- Volpicelli, J.R., Davis, M.A., & Ogin, J.E. (1986). Naltrexone blocks the post-shock increase of ethanol consumption. *Life Sciences* 38(9), 841–847.
- Volpicelli, J.R., O'Brien, C.P., Alterman, A.I., & Hayashida, M. (1990). Naltrexone and the treatment of alcohol dependence: Initial observations. In L. Reid (ed.), *Opioids, Bulimia, and Alcohol Abuse and Alcoholism*. New York: Springer-Verlag, pp. 195–214.
- Volpicelli, J.R., Alterman, A.I., Hayashida, M., & O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49(11), 876–880.
- Volpicelli, J.R., Watson, N.T., King, A.C., Sherman, C.E., & O'Brien, C.P. (1995). Effect of naltrexone on alcohol "high" in alcoholics. *American Journal of Psychiatry* 152(4), 613–615.
- Volpicelli, J.R., Rhines, K.C., Rhines, J.S., Volpicelli, L.A., Alterman, A.I., & O'Brien, C.P. (1997). Naltrexone and alcohol dependence: Role of subject compliance. *Archives of General Psychiatry* 54, 737–742.
- Wang, S.J. (2000). Statistical Consideration—exploration of multivariate failure time analysis method, an approach for alcohol treatment clinical trials. Paper presented at the *Second Seattle Symposium in Biostatistics: Analysis of Correlated Data*, Seattle, Washington.
- Weiss, F., Mitchiner, M., Bloom, F.E., & Koob, G.F. (1990). Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine, and methysergide. *Psychopharmacology* 101(2), 178–186.
- Weiss, F., Hurd, Y.L., Ungerstedt, U., Markou, A., Plotsky, P.M., & Koob, G.F. (1992). Neurochemical correlates of cocaine and ethanol self-administration. *Annals of the New York Academy of Sciences* 654, 220–241.
- Weiss, F., Lorang, M.T., Bloom, F.E., & Koob, G.F. (1993). Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. *Journal of Pharmacology and Experimental Therapeutics* 267(1), 250–258.
- Widdowson, P.S., & Holman, R.B. (1992). Ethanol-induced increase in endogenous dopamine release may involve endogenous opiates. *Journal of Neurochemistry* 59(1), 157–163.
- Wise, R.A. (1996). Neurobiology of addiction. *Current Opinion in Neurobiology* 6(2), 243–251.
- Wolfgramm, J., & Heyne, A. (1995). From controlled drug intake to loss of control: The irreversible development of drug addiction in the rat. *Behavioural Brain Research* 70(1), 77–94.
- Wolfgramm, J., Galli, G., Thimm, F., & Heyne, A. (2000). Animal models of addiction: Models for therapeutic strategies? *Journal of Neural Transmission (Budapest)* 107(6), 649–668.

- Zink, R.W., Rohrbach, K., & Froehlich, J.C. (1999). Preclinical medications development: Combining an opioid antagonist with a serotonin reuptake inhibitor produces enhanced suppression of alcohol drinking in alcohol preferring (P) rats. *Alcoholism: Clinical and Experimental Research* 23, 19A.
- Zukin, R.S., Sugarman, J.R., Fitz-Syage, M.L., Gardner, E.L., Zukin, S.R., & Gintzler, A.R. (1982). Naltrexone-induced opiate receptor supersensitivity. *Brain Research* 245(2), 285–292.

The Status of Serotonin-Selective Pharmacotherapy in the Treatment of Alcohol Dependence

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Abstract. Research performed during the past 20 years has shown that serotonin (5-hydroxytryptamine; 5-HT) neurotransmission is related to alcohol dependence. Both theoretical and empirical research have supported the idea that alcohol dependence is a chronic disease and that, in addition, biological vulnerabilities contribute to the pathogenesis of alcohol dependence. Preclinical studies have consistently demonstrated that there is a relationship between 5-HT function and alcohol consumption. Furthermore, there is evidence building that lends support for the existence of distinct alcoholic subtypes that may be differentiated by the type or complexity of their 5-HT dysfunction. Beyond excessive drinking, behaviors that are indicators of 5-HT dysregulation are depression, anxiety, impulsiveness, and early-onset problem drinking. This chapter will discuss the usefulness of 5-HT-selective pharmacotherapy in treating alcohol dependence and will provide both historical and current perspectives on its use.

1. Introduction

This chapter provides a brief overview of the rationale, history, and present status of the literature on the use of serotonin-selective medications to treat alcohol dependence. First, we summarize our understanding of the neurobiological mechanisms of serotonin (5-hydroxytryptamine; 5-HT) transmission in the etiology of alcohol dependence. Next, we present an abbreviated, historical

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perspective on the investigation of 5-HT agents to decrease excessive alcohol drinking and highlight the empirical work that has led to our current thinking. Finally, we describe the current status of 5-HT pharmacotherapy for alcohol dependence. This review will not include detailed information on individual clinical trials of 5-HT medications to reduce alcohol consumption because that information has been presented elsewhere in reviews of clinical trials conducted before the mid-1990s (Pettinati, 1996) and those after the mid-1990s (Pettinati, Oslin, & Decker, 2000a).

2. Abnormal Serotonergic Neurotransmission Linked Alcohol Dependence

It has generally been thought that the identification of biological abnormalities in chronic diseases will allow more specificity in the pharmacological interventions used to remedy those conditions. Theoretical and empirical research support the notion that alcohol dependence is a chronic disorder (McLellan, Lewis, O'Brien, & Kleber, 2000) and that biological vulnerabilities contribute to the pathogenesis of alcohol dependence (Heinz, Mann, Weinberger, & Goldman, 2001; Kranzler & Anton, 1994). Therefore, a logical extension of that literature has been scientific evaluation of medications to treat alcohol dependence.

One widely discussed area of biological vulnerabilities associated with alcohol dependence concerns neurotransmitter abnormalities. Although dopamine is the principal neurotransmitter identified with the rewarding effects of substances of abuse (Imperato & DiChiara, 1986; Mereau, Fadda, & Gessa, 1984; Wise, 1988), other neurotransmitters such as endogenous opioids, glutamate, gamma-aminobutyric acid (GABA) and 5-HT, have also been implicated in the self-administration of alcohol and other substances, directly or indirectly through dopamine (reward) modulation (Koob & Roberts, 1999; Koob & Weiss, 1992).

Several reviews have been published describing the experimental literature that links 5-HT neurotransmission to alcohol (Gorelick, 1989; Myers & Melchior, 1977; Naranjo, Sellers, & Lawrin, 1986). To summarize, both preclinical and clinical studies have consistently demonstrated an inverse relationship between 5-HT function and alcohol consumption (Banki, 1981; Carmichael & Israel, 1975; Higley, Hasert, Suomi, & Linnoila, 1998; Lovinger, 1991; Pandey, Lumeng, & Li, 1996; Roy & Linnoila, 1989; Swift, Davidson, Whelihan, & Kuznetsov, 1996; Yoshimoto, McBride, Lument, & Li, 1992).

More than 20 years ago, Ballenger and colleagues (Ballenger, Goodwin, Major, & Brown, 1979) demonstrated decreased 5-HT turnover in alcoholics, and Banki (1981) reported that the decrease in 5-HT turnover in alcoholics was correlated with the duration of their abstinence from alcohol. Subsequently, abnormally low levels of the major metabolite of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), were identified in the cerebrospinal fluid (CSF) of persons with alcohol dependence (Gorelick, 1989; Roy, Virkkunen, & Linnoila, 1990). These

results, taken together, provide evidence of a potentially "depleted" 5-HT system in alcohol dependence. Because it is known that alcohol drinking increases 5-HT release, alcohol may normalize low brain levels of 5-HT in alcohol dependence (Ballenger et al., 1979) and may play a role in reducing both the desire for and the consumption of alcohol (Naranjo & Knoke, 2001).

Another approach to examining 5-HT neurotransmission in alcoholics involves pharmacological challenges with 5-HT agonists, such as fenfluramine (Anthenelli & Maxwell, 2000; Balldin, Berggren, Engel, Eriksson, Hard, & Soderpalm, 1994; Farren, Ziedonis, Clare, Hammeedi, & Dinan, 1995) or MK-212 (Lee & Meltzer, 1991). These studies use neuroendocrine (e.g., prolactin) response as a dependent measure. Most (Balldin et al., 1994; Farren et al., 1995; Lee & Meltzer, 1991), but not all (Anthenelli et al., 2000) of these studies, have shown a blunted response to the serotonergic agent in alcoholics, compared with controls. These findings are consistent with the CSF findings, in that they demonstrate abnormal 5-HT neurotransmission in alcoholics.

The 5-HT neurotransmitter system is widespread and extends via multiple pathways in the brain and brain stem. This feature may explain why 5-HT has been implicated in a variety of human functions, including appetite, mood, arousal, impulse control, and personality traits (Coccaro & Murphy, 1990; Coccaro, Siever, Klar, Maurer, Cochrane, Cooper, Mohs, & Davis, 1989; Maes & Meltzer, 1995; Moeller, Dougherty, Swann, Collins, Davis, & Cherek, 1996). In particular, 5-HT appears to be a modulator of behavioral characteristics that overlap with alcohol dependence, such as mood and anxiety symptoms and impulse control. Low CSF 5-HIAA levels have been identified with impulsiveness, including general aggressiveness (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Linnoila, Virkkunen, Scheinin, Nuutila, Rimon, & Goodwin, 1983), as well as specific impulsive behaviors directed toward others, for example, fire setting (Virkkunen, Nuutila, Goodwin, & Linnoila, 1987), or toward self, for example, suicide (Åsberg, Schalling, & Träskman-Bendz, 1987).

In summary, there is strong evidence dating back more than 20 years that 5-HT neurotransmission is related to alcohol consumption and dependence. Based on these findings, a variety of studies have examined whether medications that target the 5-HT system may play a role in treating alcohol dependence. As this literature has developed, it has also been suggested that certain features, such as comorbid psychopathology, age of onset, and familial alcoholism risk, may differentiate subgroups of alcoholics and may interact with 5-HT medications to yield differential pharmacological responses. Data that address these specific hypotheses are presented below, following discussion of studies of the effects of 5-HT-selective agents on alcohol drinking behavior in humans.

3. Historical Overview: Trials of 5-HT-Selective Agents to Reduce Excessive Drinking

Compelling evidence of depleted 5-HT neurotransmission in alcoholics led to clinical studies of the extent to which 5-HT agents can reduce excessive

alcohol drinking (Lejoyeux, 1996). The most commonly studied 5-HT-selective agents are the reuptake inhibitors (i.e., selective serotonin reuptake inhibitors or SSRIs). A decided advantage of SSRIs in treating alcohol dependence is their safety profile, which has contributed to their widespread use for treating mood and anxiety disorders. Historically, chronic drinkers have often been denied medications (except for detoxification) due to safety concerns over the potential interaction of the medication with alcohol. However, SSRIs have low potential for abuse, do not reduce seizure threshold, do not potentiate alcohol effects on motor skills or cognition, and are relatively safe in overdose. In addition, frequency of adverse events due to these agents is relatively low; most side effects are reportedly either mild or moderate in severity. Typically, these adverse events subside when the daily dosage of the medication is reduced. Based on the safety profile of SSRIs, investigators have been more willing to examine the efficacy of these medications in patients who suffer from chronic excessive drinking.

Preclinical studies of these compounds were very encouraging: SSRIs decreased intracranial self-stimulation, an animal model that appears to provide a proxy measure for self-administration of psychoactive substances, including ethanol (Naranjo, Sellers, Roach, Woodley, Sanchez-Craig, & Sykora, 1984). In addition, a variety of 5-HT agonists (i.e., agents that produce the same effects as endogenous 5-HT) markedly reduced alcohol consumption in animals (Naranjo et al., 1986).

Based on these promising findings in animal models, a series of double-blind, placebo-controlled studies of 5-HT-selective agents were initiated by Naranjo, Sellers, and colleagues (Naranjo et al., 1984; Naranjo, Sellers, Sullivan, Woodley, Kadlec, & Sykora, 1987; Naranjo, Sullivan, Kadlec, Woodley-Remus, Kennedy, & Sellers, 1989; Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990; Sellers, Toneatto, Romach, Somer, Sobell, & Sobell, 1994). These studies examined whether a variety of SSRIs (including zimelidine, citalopram, viqueline, and fluoxetine) could reduce excessive alcohol drinking in humans. Most of these studies recruited community-based, heavy drinkers who volunteered to participate by taking a medication that might reduce their drinking. Results were consistent across these studies; modest reductions occurred in the volume of alcohol consumption from baseline. In addition, these studies showed that daily doses of SSRIs that were higher than those usually prescribed resulted in greater reductions in drinking (reviewed by Pettinati, 1996). One exception to this was a study using a 5-HT₃ antagonist, ondansetron, in which a lower dosage (0.25 mg/day compared with 2.0mg/day or placebo) resulted in a significant reduction in alcohol consumption in heavy social drinkers (Sellers et al., 1994).

In these studies, the advantage of the 5-HT-selective agents over placebo was modest [e.g., 60 mg/day of fluoxetine (a dose that is three times that generally used to treat depression) decreased daily mean alcoholic drinks from 8.7 during a baseline period to 6.9 during the 4-week trial]. However, the consistency of the results in heavy social drinkers was encouraging. Furthermore, the subjects in these studies were not seeking treatment, so presumably they

were not very motivated to reduce or stop their drinking. In addition, these subjects received no psychosocial treatment, which may be necessary to produce clinically significant reductions in drinking (Gallant, 1993; Marlatt, 1985).

The SSRI that has been studied most frequently to reduce drinking in patient populations has been fluoxetine. Fluoxetine was the first SSRI to be approved for clinical use by the U.S. Food and Drug Administration (FDA) (for treatment of major depression), so it was readily available for study. In these studies, alcohol-dependent patients were treated with 60–80 mg/day of fluoxetine (Gorelick & Paredes, 1992; Kabel & Petty, 1996; Kranzler, Burleson, Korner, Del Boca, Bohn, Brown, & Liebowitz, 1995). In contrast to the results of preclinical research and the studies in heavy social drinkers, no advantage was found for fluoxetine over placebo in reducing alcohol drinking in these studies of alcohol-dependent patients (see review by Pettinati et al., 2000a). Studies of another SSRI, citalopram, which have been conducted in Europe, have shown only modest effects of the medication on alcohol consumption in clinical studies (see Kranzler, 2000, for a review).

In summary, historically, the clinical trials conducted with SSRIs to reduce excessive alcohol drinking were moderately successful in heavy social drinkers but were negative in patient samples. However, most of these studies have not addressed the question of whether alcoholic subtypes might respond differentially to 5-HT pharmacotherapy. To test the hypothesis that 5-HT pharmacotherapy might differentially affect 5-HT functioning in alcoholics, depending upon the type or complexity of their 5-HT dysfunction, subsequent approaches sought to examine the interactive effects of alcoholism subtype and 5-HT pharmacotherapy.

4. Current Status: 5-HT Clinical Trials to Treat Subtypes of Alcohol Dependence

Recent investigations of SSRIs for treating alcohol dependence have focused on identifying whether certain subgroups of patients with alcohol dependence benefit from 5-HT-selective pharmacotherapy. Clinical characteristics that are indicators of 5-HT dysregulation (beyond excessive drinking) are depressive symptoms, anxiety symptoms, impulsiveness, early-onset problem drinking, etc. These features can be used to distinguish alcoholic subgroups by identifying the presence or absence of these types of behaviors in patients with alcohol dependence (Kranzler & Anton, 1994; Pettinati, 1996, 2001; Pettinati et al., 2000a). Two lines of inquiry that aim to accomplish this are based on psychiatric diagnosis (e.g., depression; anxiety) or etiological classifications associated with potential multiple abnormalities in 5-HT neurotransmission [e.g., early vs. late-onset alcohol dependence (Cloninger, 1987); Type A vs. B alcohol dependence (Babor, Hofmann, Del Boca, Hesselbrock, Meyer Dolinsky, & Rounsvaville, 1992b)].

4.1. Alcoholic Subtypes: Presence or Absence of Comorbid Psychiatric Disorders

4.1.1. Depressed Alcoholics and 5-HT-Selective Pharmacotherapy. Major depression, one of the most common comorbid disorders among alcoholics, makes it feasible to identify a sufficient number of alcoholics with a diagnosis of depression to construct a subgroup (Grant & Hartford, 1995; Kessler, Nelson, McGonagle, Edlund, Frank, & Leaf, 1996; Regier, Farmer, Rae, Locke, Keith, Judd, & Goodwin, 1990). In fact, in one study, the majority of female alcoholics suffered from comorbid depression (Pettinati, Rukstalis, Luck, Volpicelli, & O'Brien, 2000b). It has been shown that plasma levels of 5-HT and tryptophan are lower in depressed than in normal subjects (some of whom received alcohol), providing additional support for the idea that 5-HT neurotransmission may underlie the depressive effects of alcohol (Pietraszek, Urano, Sumioshi, Serizawa, Takahashi, Takada, & Takada, 1991). Major depression is often responsive to pharmacological treatment, and there are now a number of SSRIs with FDA approval for treating depression (e.g., citalopram, fluoxetine, paroxetine, sertraline). However, studies of these agents for treating depression have typically excluded patients with comorbid alcohol dependence, and, thus, this literature does not adequately address whether SSRIs are efficacious for treating depression in alcoholics.

The few studies in the alcoholism treatment literature that address this question have yielded mixed results. In a study of severely depressed (i.e., suicidal) alcoholics ($N = 51$) who were treated with up to 40 mg/day fluoxetine or placebo for 12 weeks, there was a significant advantage of the active drug with respect to reducing both depressive symptoms and alcohol drinking (Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase, & Black, 1997). There also was a double-blind study in which 100mg/day of sertraline for 6 weeks reduced depressive symptoms among inpatient alcoholics ($N = 36$), although given a lack of access to alcohol in this study, the medication's effects on preventing relapse to drinking were not evaluated (Roy, 1998).

In contrast to these relatively encouraging studies, there have been two preliminary negative reports of placebo-controlled studies of depressed alcoholics treated with an SSRI. In one study, depressed alcoholics ($N = 82$) were treated with up to 80mg/day of fluoxetine or placebo for 12 weeks (McGrath, 1998). In the second study, depressed alcoholics ($N = 78$) were treated with 200 mg/day of sertraline or placebo for 12 weeks (Moak, Voronin, Latham, & Anton, 2001). Although both studies reported that the SSRI provided no treatment advantage over placebo with respect to either depressive symptoms or drinking behavior, the study by Moak and colleagues suggested that there might be gender differences that obscured an effect on drinking. Last, Pettinati, Volpicelli, Luck, Kranzler, Rukstalis, and Cnaan (2001) gave 200 mg/day of sertraline or matching placebo for 14 weeks to alcohol-dependent patients with ($n = 53$) or without ($n = 47$) a lifetime history of depression. They found that the alcohol-dependent patients who benefited most from sertraline,

that is, showed the largest reductions in drinking and the greatest gains in achieving long-term abstinence, were those who had no personal or family history of depression. The fact that treatment with an SSRI was useful in a strictly defined "non" or "never" depressed subgroup of alcoholics was opposite to what was predicted. This seemingly counterintuitive finding is consistent with the decreased drinking behavior seen in other studies of SSRIs in heavy social drinkers, a group of subjects with rates of psychiatric comorbidity and other problems lower than those of typical patient samples.

4.1.2. Anxious Alcoholics and 5-HT Pharmacotherapy. Buspirone, a partial 5-HT_{1A} receptor agonist, reduces alcohol consumption in animals and reduces anxiety and alcohol consumption in alcohol-dependent humans (Collins & Myers, 1987; Engel, Fahlke, Hard, Johannessen, Svensson, & Soderpalm, 1992; Knapp & Pohorecky, 1992; Privette, Hornsby, & Myers, 1988; Roberts, McArthur, Hull, Post, & Koob, 1998; Svensson, Fahlke, Hard, & Engel, 1993). There also is an interaction of buspirone and other 5-HT_{1A} agonists with the dopamine system (Eison & Temple, 1986), which suggests that these medications might be efficacious in treating alcohol dependence. There are two positive clinical trials and one negative study of anxious alcoholics who received daily buspirone treatment. In one study, 61 patients were treated with up to 60mg/day of buspirone or placebo for 12 weeks (Kranzler, Burleson, Del Boca, Babor, Korner, Brown, & Bohn, 1994). In the second study, 51 patients received 30mg/day or 60mg/day of buspirone or placebo for 24 weeks (Tollefson, Montague-Clouse, & Tollefson, 1992). Both studies showed an advantage for buspirone over placebo in significantly reducing anxiety in this subgroup of alcoholics. Reductions in drinking were found in the first study, but drinking was not measured in the second study. In the study by Malcolm, Anton, Randall, Johnston, Brady, and Thevos (1992), there was no advantage of buspirone at a dosage of 45–60 mg/day over placebo in a sample of 67 anxious alcoholics treated for 24 weeks.

4.1.3. Summary: 5-HT Pharmacotherapy in Alcoholics with Psychiatric Disorders. In summary, the empirical findings on the value of 5-HT-selective pharmacotherapy for subgroups of alcoholics, differentiated by the presence or absence of comorbid psychiatric symptomatology, is inconsistent and needs further investigation. There is a rationale for using these agents to treat alcoholics with comorbid depression or anxiety and, in some settings, this treatment has become standard clinical care. However, the empirical data do not yet wholly support this clinical practice. A major shortcoming in the conduct of these trials is the difficulty in distinguishing symptoms that result from the neurotoxic effects of chronic heavy drinking from those that reflect an independent psychiatric disorder exacerbated by a recurrence of alcohol dependence. On the other hand, subgrouping alcoholics by the presence of comorbid psychiatric symptomatology may be a relatively inefficient method for distinguishing individuals in whom 5-HT dysfunction could translate into a positive response to 5-HT-selective pharmacotherapy.

4.2. Alcoholic Subtypes: Different Kinds of Alcohol Dependence

Several approaches to differentiating alcohol subtypes based on genetic or phenomenological features may more directly reflect differences in 5-HT function. Some of these models employ a univariate approach, for example, early-versus late-onset alcohol dependence. Others use a statistical multivariate approach designed to differentiate phenotypic profiles, for example, Type A and B alcohol dependence (Babor, Dolinsky, Rounsville, & Jaffe, 1988; Babor et al., 1992b). Both of these approaches may be useful in distinguishing patients on the basis of 5-HT dysfunction, reactivity, sensitivity, etc., which, in turn, may have important implications for the use of 5-HT-selective medications for alcohol treatment.

4.2.1. Early- versus Late-Onset Alcoholics and 5-HT-Selective Pharmacotherapy. Buydens-Branchey and colleagues (Buydens-Branchey, Branchey, & Noumair, 1989; Buydens-Branchey, Branchey, Noumair, & Lieber, 1989) found that early-onset alcoholics (excessive drinking before the age of 20) had been incarcerated more frequently for violent crimes, made more suicide attempts, and have been depressed more often than patients with a later onset of their alcohol dependence. These investigators also found that among the early-onset patients, low plasma levels of tryptophan—a precursor of 5-HT—were associated with high levels of depression and aggression.

Several investigators also examined biological aspects of alcoholic subtypes by using a pharmacological challenge paradigm. George, Benkelfat, Rawlings, Eckardt, Phillips, Nutt, Wynne, Murphy, and Linnoila (1997) administered *m*-chlorophenylpiperazine (*m*-CPP), a mixed serotonin partial agonist, to late-onset alcoholics, early-onset alcoholics with antisocial traits, and to healthy comparison subjects. They found that among alcoholics, *m*-CPP elicited differential effects: early-onset alcoholics reported more anger and anxiety, and late-onset alcoholics reported increased euphoria and a greater likelihood of drinking. Krystal, Webb, Cooney, Kranzler, and Charney (1994) found that *m*-CPP produced anxiety and "alcohol-like" effects among alcoholics (the majority of whom had early-onset of the disorder). Compared with normal controls, these alcoholics also showed a blunted cortisol response to *m*-CPP. Lee and Meltzer (1991) found that alcoholics (mainly with early-onset disorder) treated with the serotonergic agonist MK-212 reported more restlessness, irritability, and anxiety than controls.

CSF levels of 5-HIAA have also been used to differentiate alcoholic subtypes. Fils-Aime, Eckardt, George, Brown, Mefford, and Linnoila (1996) studied CSF in 131 recently abstinent alcoholics. They found that early-onset alcoholics (i.e., those with onset of excessive drinking before age 25) had a more severe course of alcoholism and lower mean CSF 5-HIAA concentration than late-onset alcoholics. Patients who had two alcoholic parents had particularly low mean CSF concentrations of 5-HIAA and tryptophan. One interpretation of these findings is that early-onset alcoholics have an abnormally low capacity to

synthesize 5-HT, which may result in an adaptive upregulation of 5-HT receptors that makes the system more sensitive to serotonergic agonist drugs.

These findings suggest that 5-HT-selective pharmacotherapy could differentially affect drinking behavior and other symptomatology in early-onset alcoholics. To date, however, there is one published clinical trial with a 5-HT-selective medication that prospectively classified patients as early-onset ($n = 161$) or late-onset ($n = 160$) alcoholics. In that study, 321 alcoholics were treated with the 5-HT antagonist, odansetron (1, 4, or 16 mcg/kg twice daily), or placebo for 11 weeks. Results showed that the greatest reductions in drinking during the trial were in the early-onset group that received 8mcg/kg/day of the medication. There were no significant differences in drinking outcomes between medication groups and placebo in the late-onset alcoholic subgroup (Johnson, Roache, Javors, DiClemente, Cloninger, Prihoda, Bordnick, Ait-Daoud, & Hensler, 2000).

4.2.2. Type A versus B Alcoholics and 5-HT-Selective Pharmacotherapy. Babor and colleagues (Babor, Dolinsky, Meyer, Hesselbrock, Hofmann, & Tennen, 1992a) used cluster analysis of data from 321 inpatient alcoholics to derive a dichotomous alcohol typology. In that typology, high-risk/severity alcoholics, referred to as "Type B," are characterized by earlier onset of problem drinking, greater Axis I and II psychopathology, higher levels of alcohol dependence severity, polydrug use, a chronic treatment history, and a poorer prognosis following treatment. In contrast, "Type A" alcoholics are characterized by a later onset of problem drinking, fewer childhood risk factors, lower levels of alcohol dependence severity, no or little drug use, fewer drinking-related problems, less psychopathology, and a better response to traditional alcoholism treatment.

The Type A/B typology resembles, in some respects, a typological approach proposed earlier by Cloninger (1987), who, based on adoption data from Sweden, distinguished Type 1 from Type 2 alcoholism. There is significant overlap between Type B and Type 2 alcoholics, as well as between Type A and Type 1 alcoholics (see comparison of traits between Babor's and Cloninger's typologies described in the review by Pettinati, 1996). However, Babor's and Cloninger's typologies also differ in some important ways. For example, in contrast to Babor's broadly defined alcoholic subtypes, Cloninger's subtypes are based primarily on personality structure and early onset of alcohol dependence. Babor's typology has also been empirically validated (Babor et al., 1992a).

There are some obvious links between Babor's typology and the clinical features that have been identified as reflecting possible 5-HT dysfunction. For example, Type B alcoholics show such features as mood symptoms, impulsivity, and aggressivity, which have been associated with 5-HT dysfunction, suggesting that this alcoholic subgroup has specific or more severe 5-HT abnormalities compared with Type A alcoholics. The 5-HT dysfunction associated with Type A alcoholics is likely to be of a more limited or less severe type, which is associated with a tendency to excessive alcohol intake. In view of the

greater evidence of 5-HT dysfunction in Type B alcoholics, it was initially hypothesized that this subgroup would benefit more from 5-HT pharmacotherapy. Interestingly, tests of this hypothesis have shown just the opposite.

There have been three randomized, placebo-controlled trials of SSRI treatment of alcoholics in which the subjects were subtyped using either Babor's or Cloninger's typology. One of the studies evaluated citalopram 40mg/day for 12 weeks for treating Type 1 ($n = 20$) and Type 2 ($n = 42$) alcoholics. There was no overall advantage of citalopram over placebo in reducing alcohol consumption, nor was there any differential advantage of citalopram in either of the subtypes (Tiihonen, Ryynanen, Kauhanen, Hakola, & Salaspuro, 1996). However, the sample size is unlikely to have yielded adequate statistical power to show an interactive effect of medication by subtype.

Two studies that used Babor's typology, assigning patients through the application of a statistical clustering procedure into Type A and B alcoholics, did find interactive effects of medication group and subtype. Kranzler, Burleson, Brown and Babor (1996) evaluated drinking outcomes in Type A ($n = 60$) and B ($n = 35$) alcoholics who had received up to 60mg/day of fluoxetine or placebo for 12 weeks. This study was a reanalysis of data that were previously analyzed for the effects of fluoxetine treatment of alcohol dependence (Kranzler et al., 1995). Though all patients reduced their drinking from pre-treatment levels, Type B alcoholics, who had characteristics suggestive of 5-HT abnormalities, showed a smaller reduction in alcohol drinking during the trial, if treated with fluoxetine, compared to those treated with placebo. In Type A alcoholics, there was a nonsignificant trend for fluoxetine to provide an advantage over placebo on some of the drinking outcomes.

A more recent double-blind, placebo-controlled study by Pettinati, Volpicelli, Kranzler, Luck, Rukstalis, and Cnaan (2000c) attempted to evaluate Kranzler and colleague's findings in a comparable treatment sample of Type A ($n = 55$) and Type B ($n = 45$) alcoholics using sertraline (up to 200mg/day) given for 14 weeks. Results supported those reported in the earlier study (Kranzler et al., 1996), that is, all patient groups significantly reduced their drinking during the trial. However, these investigators found that Type A alcoholics who received sertraline reduced their drinking significantly more and had a higher rate of total abstinence (64%) than placebo-treated patients (10% abstinence rate). This study also provided findings comparable to those of Kranzler and colleagues that Type B alcoholics drank more during the trial, if they received active treatment, compared with those receiving placebo (though this comparison did not reach statistical significance in the study by Pettinati and colleagues).

Taking these two studies of SSRI therapy in Type A and B alcoholics together, the results suggest that Type A alcoholics, who have a lower intensity of drinking and less psychopathology, may be more successful in their recovery efforts if an SSRI is added to their treatment. In contrast, an SSRI (i.e., fluoxetine or sertraline) does not provide an advantage to Type B alcoholics. It is difficult to explain why Type B alcoholics, a subgroup characterized

by multiple features associated with 5-HT dysfunction, appear either to derive no benefit from an SSRI or to show an adverse effect of the medication on drinking outcomes relative to placebo. It is possible that this subgroup has an abnormally low capacity to synthesize 5-HT, which may result in an adaptive upregulation of 5-HT receptors. This, in turn, could make the 5-HT system overly sensitive to stimulation (Lee & Meltzer, 1991). If this were true, SSRIs could aggravate the 5-HT dysfunction, rather than ameliorating it. Johnson (2000) has argued that this alcoholic subtype, which overlaps with early-onset alcoholism, may be genetically predisposed to a 5-HT transporter abnormality, which is manifest in the context of alcohol consumption. This explanation clearly goes beyond the notion of a simple 5-HT deficiency and provides a potential explanation for the 5-HT dysfunction associated with Type B alcoholism.

4.2.3. Summary: Interactive Effects of 5-HT-Selective Medications and Alcohol Subtypes. In summary, the studies reviewed above support the hypothesis that distinct forms of alcohol dependence show differential responses to 5-HT-selective medications. Interpretation of findings from these studies is limited by the comparatively sparse literature on the topic, but the most consistent observation is that subtyping alcoholics may be a fruitful approach to evaluating 5-HT-selective pharmacotherapies. For example, rather than aiming to uniformly benefit all alcoholics by 5-HT-selective pharmacotherapy, focusing on some alcoholic subtypes by prescribing higher doses of 5-HT agonists (than is the current prescribing practice) may be effective in reducing their drinking behavior. In contrast, other subtypes are unlikely to benefit from these medications.

5. Conclusions

Most of the clinical trials that have studied 5-HT-selective medications have used SSRIs. Positive effects on drinking behavior were shown in one study of fluoxetine for depressed alcoholics (although two other studies were negative) and in Type A alcoholics when treated with sertraline (one study) or fluoxetine (one study showed a nonsignificant trend). In addition, some of the trials that reported positive outcomes with 5-HT pharmacotherapy studied medications other than SSRIs, that is, the 5-HT_{1A} partial agonist, buspirone, for anxious alcoholics, and the 5-HT₃ antagonist, ondansetron, for early-onset alcoholics.

The most counterintuitive result reported was that Type B alcoholics, potentially the subgroup with the greatest evidence of 5-HT abnormalities, derived no benefit, and, in fact, may have been impeded in their recovery if they were treated with an SSRI. The lack of convincing evidence that SSRI monotherapy reduces depressive symptoms in alcoholics with comorbid major depression is also surprising, given the clear advantage that this approach has

over placebo in treating major depression in nonalcoholics. Possible explanations for these negative results, however, are the difficulty in clearly differentiating subgroups, partly due to the unreliability of a patient's recall or ability to communicate information, but also because there are inherent difficulties with each of the classifications described in this review. Some classification schemes (e.g., those based on psychiatric diagnosis) are focused on the patient's symptom profile at treatment entry and are not specific to etiology. For example, distinguishing between primary and secondary depression in alcohol-dependent patients may be "one of the most difficult diagnostic problems in psychiatry" (Gallant, 1999). Age of onset as a univariate approach to subtyping alcoholics depends on the patient's recall of the age of onset of problem drinking (or alcohol dependence, as the case may be). A multivariate approach, like Babor's or Cloninger's, can be difficult to replicate across samples and to implement in clinical practice.

In conclusion, historically, the inconsistent results from early studies of SSRIs for reducing alcohol consumption may be explained by the indiscriminate inclusion of heterogeneous groups of heavy drinkers/alcoholics. Although more recent efforts have demonstrated the utility of subtyping approaches for predicting which alcoholics may respond to 5-HT-selective pharmacotherapy, to date, this approach has not been widely employed. Future efforts to validate the findings from the current literature should also focus on establishing the reliability and validity of univariate versus multivariate approaches to subtyping alcoholics. The ultimate test of the matching hypotheses described here are studies that prospectively match alcoholic subtypes to pharmacological treatments and that reveal mechanisms whereby the medications exert their beneficial effects in some, but not all, alcoholics.

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References

- Anthenelli, R.M., & Maxwell, R.A. (2000). Cigarette smoking decreases the prolactin response to serotonergic stimulation in subgroups of alcoholics and controls. *Alcoholism: Clinical and Experimental Research* 24, 987-995.
- Åsberg, M., Schalling, D., & Träskman-Bendz, L. (1987). Psychobiology of suicide, impulsivity, and related phenomena. In H.Y. Meltzer (ed.), *Psychopharmacology: The Third Generation of Progress*. New York: Raven Press, pp. 665-668.
- Babor, T.F., Dolinsky, Z., Rounsville, B., & Jaffe, J. (1988). Unitary versus multidimensional models of alcoholism treatment outcome: An empirical study. *Journal of Studies on Alcohol* 49, 167-177.
- Babor, T.F., Dolinsky, Z., Meyer, R.E., Hesselbrock, M., Hofmann, M., & Tennen, H. (1992a). Types of alcoholics: Concurrent and predictive validity of some common classification schemes. *British Journal of Addiction* 87, 1415-1431.

- Babor, T.F., Hofmann, M., Del Boca, F.K., Hesselbrock, V., Meyer, R.E., Dolinsky, Z.S., & Rounsaville, B. (1992b). Types of alcoholics, 1: Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry* 49, 599–608.
- Ballenger, J., Goodwin, F., Major, L., & Brown, G. (1979). Alcohol and central serotonin metabolism in man. *Archives of General Psychiatry* 36, 224–227.
- Balldin, J., Berggren, U., Engel, J., Eriksson, M., Hard, E., & Soderpalm, B. (1994). Effect of citalopram on alcohol intake in heavy drinkers. *Alcoholism: Clinical and Experimental Research* 18, 1133–1136.
- Banki, C. (1981). Factors influencing monoamine metabolites and tryptophan in patients with alcohol dependence. *Journal of Neural Transmission* 50, 89–101.
- Brown, G.L., Goodwin, F.K., Ballenger, J.C., Goyer, P.F., & Major, L.F. (1979). Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research* 1, 131–139.
- Buydens-Branchey, L., Branchey, M.H., & Noumair, D. (1989). Age of alcoholism onset. I. Relationship to psychopathology. *Archives of General Psychiatry* 46, 225–230.
- Buydens-Branchey, L., Branchey, M.H., Noumair, D., & Lieber, C.S. (1989). Age of alcoholism onset. II. Relationship to susceptibility to serotonin precursor availability. *Archives of General Psychiatry* 46, 231–236.
- Carmichael, F., & Israel, Y. (1975). Effects of ethanol on neurotransmitter release by rat brain cortical slices. *Journal of Pharmacology and Experimental Therapeutics* 193, 824–834.
- Cloninger, C.R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science* 236, 410–416.
- Coccaro, E.F., & Murphy, D.L. (eds.). (1990). *Serotonin in Major Psychiatric Disorders*. Washington, DC: American Psychiatric Press.
- Coccaro, E.F., Siever, L., Klar, H.M., Maurer, G., Cochrane, K., Cooper, T.B., Mohs, R.C., & Davis, K.L. (1989). Serotonergic studies in patients with affective and personality disorders: Correlates with suicidal and impulsive aggressive behavior. *Archives of General Psychiatry* 46, 587–599.
- Collins, D.M., & Myers, R.D. (1987). Buspirone attenuates volitional alcohol intake in the chronically drinking monkey. *Alcohol and Alcoholism* 4, 49–56.
- Cornelius, J.R., Salloum, I.M., Ehler, J.G., Jarrett, P.J., Cornelius, M.D., Perel, J.M., Thase, M.E., & Black, A. (1997). Fluoxetine in depressed alcoholics: A double-blind, placebo-controlled trial. *Archives of General Psychiatry* 54, 700–705.
- Eison, A.S., & Temple, D.L. (1986). Buspirone: Review of its pharmacology and current perspectives on its mechanism of action. *American Journal of Medicine* 80 (3B), 1–9.
- Engel, J.A., Fahlke, C., Hard, E., Johannessen, K., Svensson, L., & Soderpalm, P. (1992). Serotonergic and dopaminergic involvement in ethanol intake. *Clinical Neuropharmacology* 15(Suppl 1), 64A–65A.
- Farren, C.K., Ziedonis, D., Clare, A.W., Hammeedi, F.A., & Dinan, T.G. (1995). D-fenfluramine-induced prolactin responses in postwithdrawal alcoholics and controls. *Alcoholism: Clinical and Experimental Research* 19, 1578–1582.
- Fils-Aime, M.L., Eckardt, M.J., George, D.T., Brown, G.L., Mefford, I., & Linnoila, M. (1996). Early-onset alcoholics have lower cerebral spinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. *Archives of General Psychiatry* 53, 211–216.
- Gallant, D. (1993). Amethysic agents and adjunct behavioral therapy and psychotherapy. *Alcoholism: Clinical and Experimental Research* 17, 197–198.
- Gallant, D. (1999). Alcohol. In M. Galanter & H. Kleber (eds.), *The American Psychiatric Press Textbook of Substance Abuse Treatment*, 2nd ed. Washington: American Psychiatric Press, pp. 151–164.
- George, D.T., Benkelfat, C., Rawlings, R.R., Eckardt, M.J., Phillips, M.J., Nutt, D.J., Wynne, D., Murphy, D.L., & Linnoila, M. (1997). Behavioral and neuroendocrine responses to *m*-chlorophenylpiperazine in subtypes of alcoholics and in healthy comparison subjects. *American Journal of Psychiatry* 154, 81–87.
- Gorelick, D.A. (1989). Serotonin reuptake blockers and the treatment of alcoholism. In M. Galanter (ed.), *Recent Developments in Alcoholism: Vol. 7. Treatment Research*. New York: Plenum Press, pp. 267–281.

- Gorelick, D.A., & Paredes, A. (1992). Effect of fluoxetine on alcohol consumption in male alcoholics. *Alcoholism: Clinical and Experimental Research* 16, 261–265.
- Grant, B., & Hartford, T. (1995). Comorbidity between DSM-IV alcohol use disorders and major depression: Results of a national survey. *Drug and Alcohol Dependence* 39, 197–206.
- Heinz, A., Mann, K., Weinberger, D.R., & Goldman, D. (2001). Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcoholism: Clinical and Experimental Research* 25, 487–495.
- Higley, J., Hasert, M., Suomi, S., & Linnoila, M. (1998). The serotonin reuptake inhibitor sertraline reduces excessive alcohol consumption in nonhuman primates: Effect of stress. *Neuropsychopharmacology* 18, 431–443.
- Imperato, A., & DiChiara, G. (1986). Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. *Journal of Pharmacology and Experimental Therapeutics* 239, 219–228.
- Johnson, B.A. (2000). Serotonergic agents and alcoholism treatment: Rebirth of the subtype concept—a hypothesis. *Alcoholism: Clinical and Experimental Research* 24, 1597–1601.
- Johnson, B.A., Roache, J.D., Javors, M.A., DiClemente, C.C., Cloninger, C.R., Prihoda, T.J., Bordnick, P.S., Ait-Daoud, N., & Hensler, J. (2000). Odansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *Journal of the American Medical Association* 284(9), 963–971.
- Kabel, D., & Petty, F. (1996). A double-blind study of fluoxetine in severe alcohol dependence: Adjunctive therapy during and after inpatient treatment. *Alcoholism: Clinical and Experimental Research* 20, 780–784.
- Kessler, R.C., Nelson, C.B., McGonagle, K.A., Edlund, M.J., Frank, R.G., & Leaf, P.J. (1996). The epidemiology of co-occurring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry* 66, 17–31.
- Knapp, D.J., & Pohorecky, L.A. (1992). Zaconpride, a 5-HT₃ receptor antagonist, reduces voluntary ethanol consumption in rats. *Pharmacology, Biochemistry and Behavior* 41, 847–850.
- Koob, G., & Roberts, A. (1999). Brain reward circuits in alcoholism. *CNS Spectrums* 4, 23–37.
- Koob, G., & Weiss, F. (1992). Neuropharmacology of cocaine and ethanol dependence. *Recent Developments in Alcoholism* 10, 201–233.
- Kranzler, H.R. (2000). Pharmacotherapy of alcoholism: Gaps in knowledge and opportunities for research. *Alcohol and Alcoholism* 35, 537–547.
- Kranzler, H.R., & Anton R.F. (1994). Implications of recent neuropsychopharmacologic research for understanding the etiology and development of alcoholism. *Journal of Consulting and Clinical Psychology* 62, 1116–1126.
- Kranzler, H.R., Burleson, J.A., Del Boca, F.K., Babor, T.F., Korner, P., Brown, J., & Bohn, M.J. (1994). Buspirone treatment of anxious alcoholics: A placebo-controlled trial. *Archives of General Psychiatry* 51(9), 720–731.
- Kranzler, H.R., Burleson, J.A., Korner, P., Del Boca, F.K., Bohn, M.J., Brown, J., & Liebowitz, N. (1995). Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. *American Journal of Psychiatry* 152(3), 391–397.
- Kranzler, H.R., Burleson, J.A., Brown, J., & Babor, T.F. (1996). Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcoholism: Clinical and Experimental Research* 20, 1534–1541.
- Krystal, J.H., Webb, E., Cooney, N.L., Kranzler, H.R., & Charney, D.S. (1994). Specificity of ethanol-like effects elicited by Serotonergic and noradrenergic mechanisms. *Archives of General Psychiatry* 51, 898–911.
- Lee, M.A., & Meltzer, H.Y. (1991). Neuroendocrine responses to Serotonergic agents in alcoholics. *Biological Psychiatry* 30, 1017–1030.
- Lejoyeux, M. (1996). Use of serotonin (5-hydroxytryptamine) reuptake inhibitors in the treatment of alcoholism. *Alcohol and Alcoholism* 1, 69–75.
- Linnoila, M., Virkkunen, M., Scheinin, M., Nuutila, A., Rimon, R., & Goodwin, F.K. (1983). Low cerebrospinal fluid 5-Hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sciences* 33, 2609–2614.
- Lovinger, D. (1991). Ethanol potentiation of 5-HT₃ receptor-mediated ion current in NCB-20 neuroblastoma cells. *Neuroscience Letters* 122, 57–60.

- Maes, M., & Meltzer, H. (1995). The serotonin hypothesis of major depression. In A.C. Bloom & D.J. Kupfer (eds.), *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press, pp. 933–944.
- Malcolm, R., Anton, R.F., Randall, D.L., Johnston, A., Brady, K., & Thevos, A. (1992). A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcoholism: Clinical and Experimental Research* 16, 1007–1013.
- Marlatt, G.A. (1985). Relapse prevention: Theoretical rationale and overview of the model. In G.A. Marlatt & J.R. Gordon (eds.), *Relapse Prevention*. New York: Guilford, pp. 3–70.
- McGrath, P. Fluoxetine for the treatment of alcoholism and depression. In R. Litten (Chair), Does 5-HT pharmacotherapy have a role in alcohol treatment? Symposium conducted at the *Annual Meeting of the Research Society on Alcoholism*, Hilton Head, SC, June 1998.
- McLellan, A.T., Lewis, D.C., O'Brien, C.P., & Kleber, H.D. (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association* 284(13), 1689–1695.
- Mereau, G., Fadda, F., & Gessa, G. (1984). Ethanol stimulates the firing rate of nigral dopaminergic neurons in unanesthetized rats. *Brain Research* 292, 63–69.
- Moak, D.H., Voronin, K.E., Latham, P.K., & Anton, R.F. (2001). A double-blind placebo-controlled treatment study of sertraline in depressed alcoholics: Preliminary analysis. *Alcoholism: Clinical and Experimental Research* 25, 94A.
- Moeller, F.G., Dougherty, D.M., Swann A.C., Collins, D., Davis, C.M., & Cherek, D.R. (1996). Tryptophan depletion and aggressive responding in healthy males. *Psychopharmacology* 126, 97–103.
- Myers, R., & Melchior, C.L. (1977). Alcohol and alcoholism: Role of serotonin. In W.B. Essman (ed.), *Serotonin in Health and Disease: Vol. 2. Physiological Regulation and Pharmacological Action*. New York: Spectrum, pp. 373–430.
- Naranjo, C.A., & Knoke, D.M. (2001). The role of selective serotonin reuptake inhibitors in reducing alcohol consumption. *Journal of Clinical Psychiatry* 62(Suppl 20), 18–25.
- Naranjo, C.A., Sellers, E.M., Roach, C.A., Woodley, D.V., Sanchez-Craig, M., & Sykora, K. (1984). Zimelidine-induced variations in alcohol intake by nondepressed heavy drinkers. *Clinical Pharmacology & Therapeutics* 35, 373–381.
- Naranjo, C.A., Sellers, E.M., & Lawrin, M. (1986). Modulation of ethanol intake by serotonin uptake inhibitors. *Journal of Clinical Psychiatry* 47(Suppl 4), 16–22.
- Naranjo, C.A., Sellers, E.M., Sullivan, J.T., Woodley, D.V., Kadlec, K., & Sykora, K. (1987). The serotonin uptake inhibitor citalopram attenuates ethanol intake. *Clinical Pharmacology & Therapeutics* 41, 266–274.
- Naranjo, C.A., Sullivan, J.T., Kadlec, K.E., Woodley-Remus, D.V., Kennedy, G., & Sellers, E.M. (1989). Differential effects of viqualine on alcohol intake and other consummatory behaviors. *Clinical Pharmacology & Therapeutics* 46, 301–309.
- Naranjo, C.A., Kadlec, K.E., Sanhueza, P., Woodley-Remus, D., & Sellers, E.M. (1990). Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clinical Pharmacology & Therapeutics* 47, 490–498.
- Pandey, S., Lumeng, L., & Li, T. (1996). 5HT-2C receptors and 5HT-2C receptor-mediated phosphoinositide hydrolysis in the brain of alcohol-preferring and alcohol-non-preferring rats. *Alcoholism: Clinical and Experimental Research* 20, 1038–1042.
- Pettinati, H.M. (1996). Use of serotonin selective pharmacotherapy in the treatment of alcohol dependence. *Alcoholism: Clinical and Experimental Research* 20(7, Suppl), 23A–29A.
- Pettinati, H.M. (2001). The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. *Journal of Clinical Psychiatry* 62(Suppl 20), 26–31.
- Pettinati, H.M., Oslin, D., & Decker, K. (2000a). Role of serotonin and serotonin-selective pharmacotherapy in alcohol dependence. *CNS Spectrums* 5(2), 33–46.
- Pettinati, H.M., Rukstalis, M.R., Luck, G.J., Volpicelli, J.R., & O'Brien, C.P. (2000b). Gender and psychiatric comorbidity: Impact on clinical presentation of alcohol dependence. *American Journal on Addictions* 9, 242–252.
- Pettinati, H.M., Volpicelli, J.R., Kranzler, H.R., Luck, G., Rukstalis, M.R., & Cnaan, A. (2000c). Sertraline treatment for alcohol dependence: Interactive effects of medication and subtype. *Alcoholism: Clinical and Experimental Research* 24(7), 1041–1049.

- Pettinati, H.M., Volpicelli, J.R., Luck, G., Kranzler, H.R., Rukstalis, M.R., & Cnaan, A. (2001). Double-blind clinical trial of sertraline treatment for alcohol dependence. *Journal of Clinical Psychopharmacology* 21(2), 143–153.
- Pietraszek, M.H., Urano, T., Sumioshi, K., Serizawa, K., Takahashi, S., Takada, Y., & Takada, A. (1991). Alcohol-induced depression: Involvement of serotonin. *Alcohol and Alcoholism* 26(2), 155–159.
- Privette, T.H., Hornsby, R.I., & Myers, R.D. (1988). Buspirone alters alcohol drinking induced in rats by tetrahydropapaveroline injected into brain monoaminergic pathways. *Alcohol* 5, 147–152.
- Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., & Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 264, 2511–2518.
- Roberts, A.J., McArthur, R.A., Hull, E.E., Post, C., & Koob, G.F. (1998). Effects of amperozide, 8-OH-DPAT, and FG5974 on operant responding for ethanol. *Psychopharmacology* 137, 25–32.
- Roy, A. (1998). Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. *Biological Psychiatry* 44, 633–637.
- Roy, A., & Linnoila, M. (1989). CSF studies on alcoholism and related behaviors. *Progress In Neuropsychopharmacology & Biological Psychiatry* 13, 505–511.
- Roy, A., Virkkunen, M., & Linnoila, M. (1990). Serotonin in suicide, violence, and alcoholism. In E.F. Coccaro & D.L. Murphy (eds.), *Serotonin in Major Psychiatric Disorders*. Washington, DC: American Psychiatric Press, pp. 187–208.
- Sellers, E., Toneatto, T., Romach, M., Somer, G., Sobell, L., & Sobell, M. (1994). Clinical efficacy of the 5-HT₃ antagonist ondansetron in alcohol abuse and dependence. *Alcoholism: Clinical and Experimental Research* 18, 879–885.
- Svensson, L., Fahlke, C., Hard, E., & Engel, J.A. (1993). Involvement of the serotonergic system in ethanol intake in the rat. *Alcohol* 10, 219–224.
- Swift, R., Davidson, D., Whelihan, W., & Kuznetsov, O. (1996). Ondansetron alters human alcohol intoxication. *Biological Psychiatry* 40, 514–521.
- Tiihonen, J., Ryynanen, O.P., Kauhanen, J., Hakola, H.P.A., & Salaspuro, M. (1996). Citalopram in the treatment of alcoholism: A double-blind placebo-controlled study. *Pharmacopsychiatry* 29, 27–29.
- Tollefson, G.D., Montague-Clouse, J., & Tollefson, S.L. (1992). Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). *Journal of Clinical Psychopharmacology* 12, 19–26.
- Virkkunen, M., Nuutila, A., Goodwin, F.K., & Linnoila, M. (1987). Cerebrospinal fluid monoamine metabolite levels in male arsonists. *Archives of General Psychiatry* 44, 241–247.
- Wise, R. (1988). The neurobiology of craving: Implications for the understanding and treatment of addiction. *Journal of Abnormal Psychology* 97, 118–132.
- Yoshimoto, K., McBride, W.J., Lument, L., & Li, T.K. (1992). Ethanol enhances the release of dopamine and serotonin in the nucleus accumbens of HAD and LAD lines of rats *Alcoholism: Clinical and Experimental Research* 16, 781–785.

Animal Models of Motivation for Drinking in Rodents with a Focus on Opioid Receptor Neuropharmacology

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Many different animal models have been proposed for developing medications to treat alcoholism, but few models have been tested to date for predictive validity. This chapter will explore models of positive reinforcement that have proven predictive validity for developing medications to treat alcoholism. To explore the validation of these models, the second part of the chapter will explore the independent variables that have been used to show how manipulation of the opioid peptide neurotransmitter system, long implicated in the motivation for drinking, affects drinking in these models. To accomplish these goals and to provide the most complete picture of the models in the context of a specific domain, brain opioid peptide systems have been chosen to elaborate the important issues. More is known preclinically about opioid antagonists, and naltrexone was the first medication to be used clinically since the development of disulfiram (*Antabuse*^R). Finally, the use of opioid peptide systems to illustrate the value of animal models will allow generating hypotheses about future medications in this specific domain.

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1. Positive Reinforcement Animal Models for Development of Medications to Treat Alcoholism

Animal models with predictive validity for medications development have centered largely on animal models for the positive reinforcing effects of ethanol. An early barrier to such models was the aversive taste of high concentrations of ethanol in rodents, a phenomenon shared by humans without experience of ethanol. Overcoming the aversive taste of ethanol was required to induce the drinking of sufficient quantities of ethanol to produce a state of intoxication. As pioneered by Herman Samson and colleagues (Samson, 1986), a series of studies has shown that introducing ethanol in a sweet solution and then fading out the sweet solution produces reliable ethanol intake in 6 to 8 weeks (Samson, 1986; Weiss, Mitchiner, Bloom, & Koob, 1990) (Fig. 1).

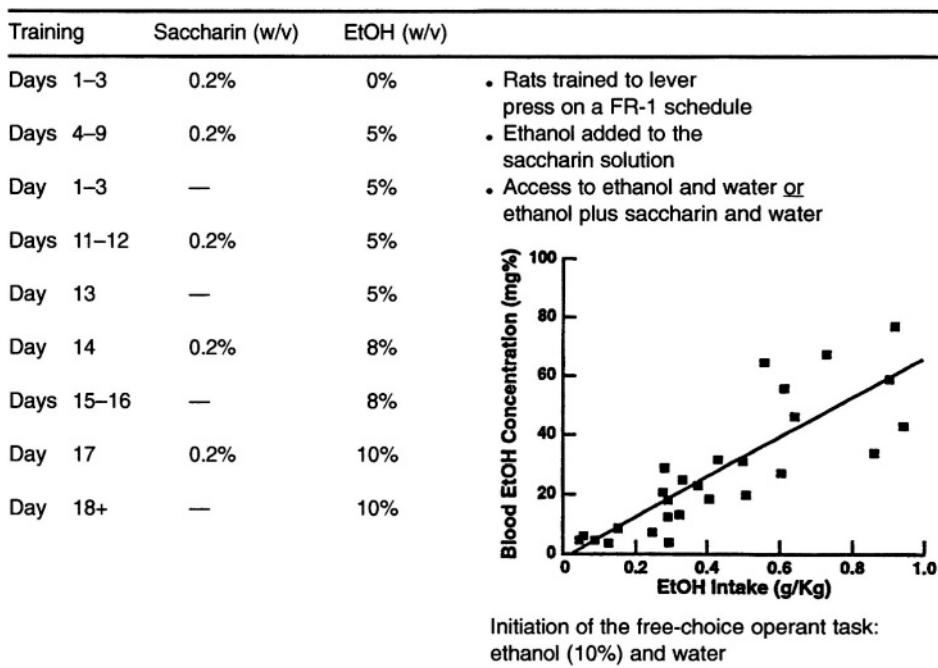


Figure 1. The table on the left represents a protocol for initiating lever pressing for oral ethanol self-administration in the rat using the saccharin fading procedure. The graph on the right shows blood ethanol concentrations as a function of ethanol intake during a baseline session in the two-lever, free-choice operant task. The variation in these measures in this distribution reflects the nature of responding that typically is observed in a group of nonselected heterogeneous Wistar rats (taken with permission from Rassnick, Pulvirenti, & Koob, 1993).

1.1. Two-Bottle Choice Procedure—Rats

Two-bottle choice ethanol self-administration involves allowing rats to drink freely from both a bottle containing water and one containing an ethanol solution. Ethanol intake as well as preference for ethanol (ethanol intake over total fluid intake) can be determined. Both unlimited (24 hour) and limited (shorter period) access are employed, often depending on the particular experimental question involved. Rats genetically selected for ethanol preference typically will consume unsweetened ethanol without any special induction process (e.g., Froehlich, 1995). However, standard rat strains generally require either a sweetened solution fading procedure or a gradual increase in ethanol concentrations (or simultaneous exposure to several concentrations of ethanol; see Spanagel & Holter, 1999) before they will consume significant quantities of unadulterated ethanol. In the sweetened solution fading procedure (modified from Samson, 1986), rats are exposed to a bottle containing water and another containing increasing concentrations of sweetened ethanol (Gauvin, Moore, & Holloway, 1993). Then, the sweetener is removed so that ultimately the rats are voluntarily consuming an unadulterated ethanol solution. Another common means to acclimate rats to ethanol involves allowing them access to gradually increasing ethanol concentrations (Veale, 1973). For example, Stromberg and colleagues (Stromberg, Mackler, Volpicelli, & O'Brien, 2001) used continuous exposure to ascending ethanol concentrations of 2, 4 and 6% before ultimately exposing the rats to a limited access testing period. Some investigators choose to leave a sweetener in or even employ some form of food or fluid deprivation to enhance ethanol intakes. However, these manipulations may result in overshadowing ethanol's motivational effects by taste or caloric need (Cunningham, Fidler, & Hill, 2000).

1.2. Two-Bottle Choice Procedure—Mice

The procedures used for two-bottle choice training and testing of mice are very similar to those used for rats. The precise procedure used to examine ethanol self-administration varies depending on the experimental question and the mouse strains used. In one general paradigm, mice are allowed access to two bottles (one containing 2, 5, 8, 10, 15, or 20% ethanol and the other containing water) for 24-hour periods. The ethanol concentration used may be constant (eg., 1 week of access to 10% ethanol vs. water) or may be gradually increased, as described above for rats. Such procedures have been used widely for comparing mice of different genetic backgrounds. For example, C57/BL6J mice will consume more ethanol at each of these concentrations than DBA/2J mice (Crabbe, Phillips, Cunningham, & Belknap, 1992). The other general procedure involves sweetened solution fading, as discussed above for rats. In addition, as with rats, the two-bottle choice test sessions can vary from 30 minutes per day to unlimited access across many days.

1.3. Limited Access Operant Self-Administration—Rats

Rats are trained to lever press for ethanol using a saccharin fading procedure adapted from a sweetened solution procedure developed by Samson (1987). This paradigm, it has been shown, produces lever pressing behavior and ethanol consumption that results in pharmacologically relevant blood alcohol levels. Rats are restricted to 3 hours of water for 3 days and are allowed access to the operant boxes where responding on the one extended lever results in the delivery of a saccharin solution. Thereafter, water restriction is discontinued. Ethanol concentrations increase from 5% to 8% to a final concentration of 10% during the next 20 days; each concentration is first mixed with saccharin and then presented alone. (see Fig. 1) During this saccharin fading procedure, both levers are extended; one lever produces ethanol/saccharin, and the other produces water. Responses on the water lever allow investigating nonspecific decreases in responding. The levers associated with each solution generally are alternated between left and right positions on consecutive days. Rats are allowed to respond for 10% ethanol versus water for 4 to 6 weeks (until responding across 3 consecutive days varies less than 25% and preference for ethanol over water is at least 60%) before test sessions are conducted. Operant sessions are typically 30 minutes long during the training and testing phases and are conducted 5 days per week at the same time each day.

Using this procedure, rats typically respond for ethanol in a 30-minute session to yield blood alcohol levels of 25–30 mg% (Roberts, Heyser, & Koob, 1999). These levels of consumption do not systematically increase from day to day and are stable across continuous testing. The advantages of this procedure as an initial screen are that the behavior is stable, the animals are performing a task to obtain the ethanol, and there are controls for nonspecific effects. Using the opioid models, this approach has led to testable hypotheses regarding opioid antagonists as potential treatments for alcoholism.

1.4. Limited Access Operant Self-Administration—Mice

A similar saccharin fading procedure is used to establish ethanol as a reinforcer in mice. Operant ethanol self-administration may involve either nosepoke responding or lever pressing behavior. Responding on one manipulandum results in the delivery of saccharin/ethanol, and responding on the other manipulandum results in the delivery of water. An example of the progression of saccharin fading training is as follows: 10 days of saccharin versus water; 6 days of 5% ethanol plus saccharin versus water; 4 days of 5% ethanol; 4 days of 8% ethanol plus saccharin versus water; 4 days of 8% ethanol; 12 days of 10% ethanol plus saccharin versus water. Ultimately, unsweetened 10% ethanol and water are available.

As with rats, 30-minute operant sessions typically result in blood alcohol levels of approximately 20–30 mg% (Roberts, McDonald, Heyser, Kieffer, Matthes, Koob, & Gold, 2000; Roberts, Gold, Polis, McDonald, Filliol, Kieffer, & Koob, 2001). This procedure has been used successfully to investigate the role of the opioid peptide system in the rewarding effects of ethanol using genetically engineered mice (see below).

1.5. Drinking in Alcohol-Preferring Rats

Ethanol studies with inbred lines and selected breeding have established a number of selected lines for high ethanol consumption that have been based on the phenotype of free-choice drinking. Numerous lines of rats and mice have been selected and characterized (Li, Lumeng, & Doolittle, 1993). For rats, these lines include alcohol-preferring (P) and alcohol nonpreferring (NP), high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD), Sardinian alcohol-preferring (SP) and Sardinian nonpreferring (SNP), and Alko alcohol (AA) and Alko nonalcohol (ANA). For mice, these lines include high alcohol-preferring (HAP) and low alcohol-preferring (LAP). For both rats and mice, these alcohol-preferring animals in general tend to have low sensitivity to ethanol and innate differences in neurotransmitter systems known to be involved in the positive reinforcing effects of ethanol such as serotonin and dopamine (McBride & Li, 1998). Several studies have shown that alcohol intake in these animals is modified by sensitive to opioid antagonists.

2. Alcohol Deprivation Effect

An animal model for the enhanced motivation to seek ethanol associated with heavy drinking derives from rich literature on the ethanol deprivation effect

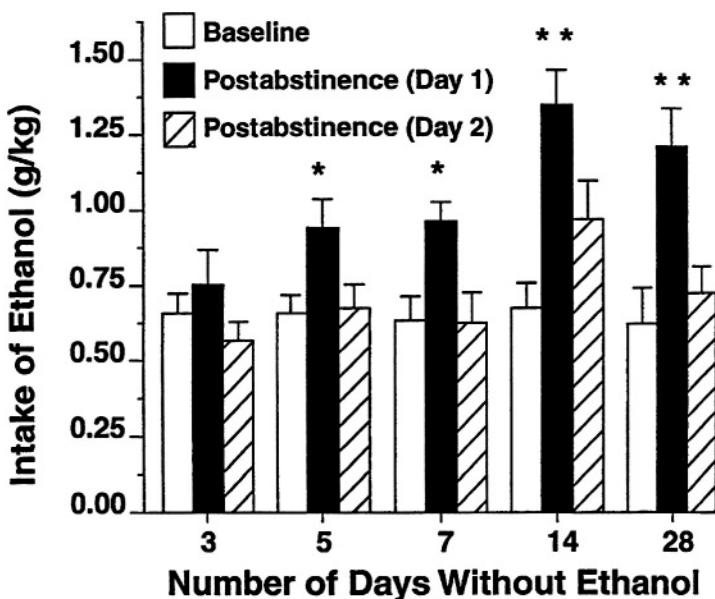


Figure 2. Mean total intake of ethanol in grams per kilogram during a 30-minute limited access operant session. Ethanol intake increased as a function of the duration of ethanol deprivation. This increase was temporary and returned to baseline levels in 2 to 3 days. Data are presented as means \pm SEM. * $p < .05$, significantly greater than baseline. ** $p < .005$, significantly greater than baseline and groups deprived of ethanol for 3, 5 or 7 days (taken with permission from Heyser et al., 1997).

where animals subjected to forced abstinence from regular drinking show an overshoot in drinking when ethanol is again available (Sinclair & Senter, 1967, 1968; Sinclair, 1979). Using an operant procedure, animals trained to self-administer ethanol using the saccharin fading procedure and then baselined on daily sessions showed a 30–40% increase in ethanol self-administration following imposed abstinence of 5 days or more (Heyser, Schulteis, & Koob, 1997) (Fig. 2). This ethanol deprivation effect is very reliable and has some predictive validity.

There are only two psychotropic medications currently on the market for preventing relapse in alcoholism: naltrexone and acamprosate. Both naltrexone and acamprosate, given daily two times a day for 5 days, block the increase in responding for ethanol produced by abstinence (Heyser, Schulteis, Durbin, & Koob, 1998; Heyser, Moc, Roberts, & Koob, 2000). Both drugs at the low dose ranges blocked the increase in responding without affecting baseline responding. Others have seen identical effects using more long-term access drinking models (Spanagel, Holter, Allingham, Landgraf, & Zieglgansberger, 1996). These results suggest that the excessive ethanol consumption associated with deprivation may provide a useful model for testing unknown compounds with potential as anticraving and antirelapse medications.

3. Conditioned Reinforcement: Discriminative Stimulus (Cue)-Induced Reinstatement of Self-Administration

Stimuli associated with the availability or consumption of drugs can evoke subjective feelings of craving in humans and trigger episodes of relapse in abstinent alcoholics (Robbins & Ehrman, 1992). For example, abstinent alcohol users in a bar-like situation worked harder to obtain alcohol than individuals in a neutral environment (Ludwig & Stark, 1974). It has been shown that alcohol-related environmental cues have motivational significance in animal studies if the cues served as discriminative stimuli previously predictive of alcohol availability (Katner & Weiss, 1999; Katner, Magalang, & Weiss, 1999).

Wistar rats were trained to lever press for oral administration of 10% ethanol (as described above) or a 50 µM quinine hydrochloride solution in the presence of distinct olfactory cues that signaled the availability of each solution. In one group of animals, the odor of banana extract served as the S⁺ (ethanol-associated) discriminative stimulus, and the odor of orange extract served as the S⁻ (quinine-associated) discriminative stimulus. In another group of animals, the odor of ethanol itself served as the S⁺ (ethanol-associated) discriminative stimulus, and the odor of the quinine solution served as the S⁻ (quinine-associated) discriminative stimulus. Then, rats were subjected to an extinction phase where lever presses had no scheduled consequences. After extinction, the animals were exposed to the respective olfactory cues without the availability of ethanol or quinine. Presentation of olfactory cues associated with ethanol, but not quinine-associated cues, significantly reinstated lever pressing behavior in the absence of ethanol as the primary reinforcer (Katner & Weiss, 1999) (Fig. 3). A similar procedure with

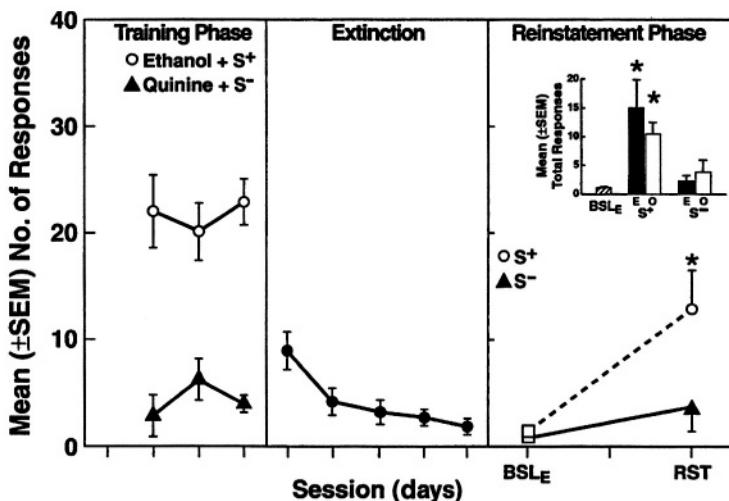


Figure 3. Mean (\pm SEM) lever presses per 30-min session during training, extinction, and reinstatement phases in male Wistar rats ($n = 24$). Training Phase: Responses for 10% (w/v) ethanol or 50 μ M quinine hydrochloride (S^-) in the presence of distinct discriminative stimuli (S) signaling the availability of ethanol (S^+) or quinine (S^-). Only responses during the final 3 days of the self-administration training/microdialysis habituation phase are shown. Extinction Phase: Mean (\pm SEM) extinction responses per 30-min session. Withholding of ethanol (and quinine) as well as the corresponding S 's resulted in extinction of responding, as defined by a criterion of ≤ 5 responses/session during 3 consecutive days. All rats reached the extinction criterion within 15 days (only mean responses during the first 5 days of this phase are shown). Reinstatement phase: lever-press responses in rats exposed to the S^+ and S^- conditions without availability of ethanol or quinine. BSL_E : mean "baseline" extinction responses as measured 3 days before the beginning of reinstatement tests. BSL_E tests were conducted after completion of the 15-day extinction training period plus an additional time period during which animals were confined to their home cages until reinstatement testing. The mean (\pm SEM) total time between the final ethanol self-administration session and first reinstatement test was 26.9 ± 2.5 days. Responses (pooled across the respective olfactory S conditions; see inset) during presentation of the ethanol S 's (S^+) differed from responding in the presence of the quinine nonreward S 's (S^-) as well as from BSL_E responses ($*p < .001$). Inset: comparison of mean "baseline" extinction responses (BSL_E) with responses elicited by the discriminative stimuli for ethanol (S^+) and quinine (S^-) under the fruit extract (E) versus solution odor (O) olfactory conditions ($*p < .05$) (taken with permission from Katner & Weiss, 1999).

auditory cues predicting ethanol availability failed to reinstate responding, which suggests salience of olfactory cues for ethanol (Katner et al., 1999).

Similar effects were observed in the alcohol-preferring P and NP rats using a banana extract as the S^+ discriminative stimulus and anise odor as the S^- discriminative stimulus (Ciccocioppo, Angeletti, & Weiss, 2001). In addition, each lever press for ethanol was associated with the presentation of the house light conditioned stimulus (CS^+) and each lever press for water was associated with

a brief white noise presentation (CS^-). Ethanol-reinforced responding was greater in P than in NP rats, and after extinction, a significant recovery of responding was observed in both groups with presentation of the S^+/CS^+ but not the S^-/CS^- that was associated with water. However, the response reinstatement was greater in P than in NP rats (Ciccocioppo et al., 2001).

4. Independent Variables Used to Predict Medications for Treating Alcoholism—The μ -Opioid System as a Prototype

4.1. Selective Antagonists

Naloxone and naltrexone, nonselective opioid receptor antagonists (meaning they are not selective for any particular opioid receptor subtype), reduce ethanol consumption in humans (O'Malley, Jaffe, Chang, Schottenfeld, Meyer, & Rounsville, 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992), animals (Ulm, Volpicelli, & Volpicelli, 1995; Rodefer, Campbell, Cosgrove, & Carroll, 1999), and rodents (Weiss et al., 1990; Reid & Hunter, 1984; Stromberg, Casale, Volpicelli, Volpicelli, & O'Brien, 1998), lending some support to the predictive validity of animal models of ethanol consumption with regard to opioid neuropharmacology. The growing availability of more selective opiate receptor antagonists has allowed researchers to examine more specifically the role of μ -opioid receptors in ethanol consumption using a pharmacological approach. For example, the μ -receptor antagonist β -funaltrexamine decreased ethanol drinking in genetically heterogeneous Wistar (Stromberg et al., 1998) and HAD rats (Froehlich, 1995). These data, therefore, provide pharmacological evidence for a role of μ -opioid receptors in ethanol drinking behavior.

4.2. Effects of Opioid Antagonists on Self-Administration of Ethanol in Alcohol-Preferring Rats

General opioid receptor antagonists decrease ethanol consumption in ethanol-preferring rats (P rats, HAD rats, and AA rats). Naloxone, naltrexone, and nalmefene all decrease self-administration (June, Grey, Warren-Reese, Durr, Ricks-Cord, Johnson, McCane, Williams, Mason, Cummings, & Lawrence, 1998; Hyttia & Sinclair, 1993; Weiss et al., 1990). Some studies have shown that this effect is selective for ethanol, but in general, these antagonists also decrease responding for sweet solutions as well, though sometimes at higher doses (Biggs & Myers, 1998; June, McCane, Zink, Portoghese, Li, & Froehlich, 1999). Perhaps more interesting, selective μ -opioid receptor antagonists also are effective in decreasing ethanol self-administration. β -Funaltrexamine decreased ethanol intake but not water intake in HAD rats (Krishnan-Sarin, Wand, Li, Portoghese, & Froehlich, 1998), and the μ antagonist D-Phe-Cys-Tyr-D-Orn-Thr-Pen-Thr-Pen-Thr-NH₂ (CTOP) also decreased ethanol consumption in AA rats (Hyttia, 1993). Naloxonazine, the μ_1 -opioid receptor antagonist, had transient effects in decreasing ethanol self-administration in AA rats

(Alko alcohol) (Honkanen, Vilamo, Wegelius, Sarviharju, Hyttia, & Korpi, 1996). The results with selective δ -receptor antagonists are not nearly as consistent. Although it has been shown that the δ -selective antagonists, naltriben, naltrindole, and ICI 174,864, decrease self-administration of ethanol in alcohol-pre-ferring rats (Krishnan-Sarin, Jing, Kurtz, Zweifel, Portoghese, Li, & Froehlich, 1995a; June et al., 1999), other studies have failed to see changes in ethanol self-administration in alcohol-preferring rats with [D -Pen², D -Pen⁵]enkephalin (Honkanen et al., 1996), or with ICI 174,894 (Hyttia, 1993).

4.3. Effects of Chronic Naltrexone Administration on the Alcohol Deprivation Effect

The opioid receptor antagonist naltrexone decreases ethanol self-administration under various conditions of positive reinforcement for ethanol. In one experiment, the goal was to examine the effects of chronic low doses of naltrexone on the increased ethanol self-administration associated with deprivation. It has been proposed that a deprivation-induced increase in drinking may be related to "loss of control," which may have implications for relapse. Forty-eight male Wistar rats were trained to lever press for ethanol. Following establishment of stable responding for ethanol, a 5 day deprivation period was imposed during which ethanol was not available. During this period of ethanol deprivation, rats remained in their home cages with food and water available *ad libitum*. Each animal received chronic (twice daily) subcutaneous injections of saline or naltrexone for 5 days. Injections of saline or naltrexone (0.06, 0.125, or 0.25 mg/kg, $n = 12$ per group) were made at 12-hour intervals at approximately 6:00 AM and 6:00 PM. Animals were tested 30 minutes after the last injection on Day 5. Saline-treated animals deprived of ethanol for 5 days significantly increased their responding for ethanol compared to baseline levels of responding. In contrast, no increase in responding for ethanol was observed in animals chronically treated with naltrexone. The effects of naltrexone on ethanol deprivation were selective for ethanol, and no significant alterations in responding for water were observed. These results suggest that chronic administration of naltrexone eliminated the ethanol deprivation effect and support the use of this naltrexone treatment strategy in our model of ethanol self-administration following protracted abstinence from chronic ethanol exposure.

4.4. Effects of Naltrexone on Responding to Ethanol-Associated Cues

Naltrexone selectively attenuated the reinstatement of responding produced by presentation of the discriminative olfactory/visual stimuli associated with the availability of ethanol in a conditioned reinforcement model (Fig. 4). Naltrexone had no effect on the responding associated with presentation of the discriminative olfactory/visual stimuli associated with the availability of water. Administration of the δ -selective opioid receptor antagonist naltrindole or the μ -selective opioid receptor antagonist naloxonazine significantly attenuated ethanol-seeking behavior in the S^+/CS^+ condition. However, these agents

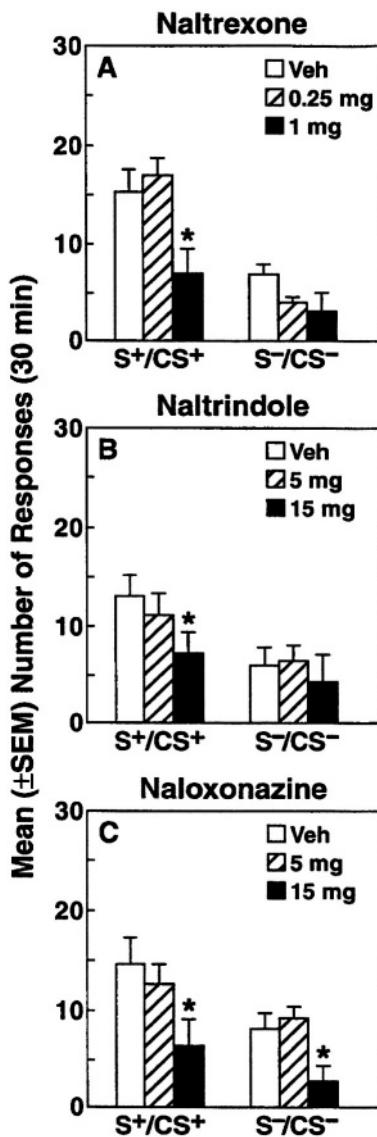


Figure 4. Attenuation of three opiate antagonists of ethanol-seeking behavior in the S⁺/CS⁺ condition. Naltrexone significantly ($p < .05$) decreased responding at the 1 mg/kg dose (Newman-Keuls following overall ANOVA: $F[2,6] = 4.09$, $p < .05$). Specifically, at this dose, lever pressing decreased by approximately 60% from 16.57 ± 2.05 (vehicle) to 7.00 ± 2.14 . Naltrexone did not alter responding in the S⁻/CS⁻ condition at any dose ($F[2,6] = 3.07$; ns). The δ -opioid receptor antagonist naltrindole also attenuated responding in the S⁺/CS⁺ condition ($F[2,6] = 4.58$, $p < .05$). Posthoc comparisons indicated that the inhibition of responding was significant at the highest dose (5 mg/kg) of the drug ($p < .05$). Responding at this dose was reduced by about 50% from 12.57 ± 2.30 (vehicle) to 7.28 ± 1.89 . Naltrindole did not modify lever pressing behavior in the S⁻/CS⁻ test condition ($F[2,6] = 0.21$; ns). A significant overall treatment effect of the μ_1 -selective opioid antagonist naloxonazine was observed under both the S⁺/CS⁺ ($F[2,6] = 4.22$, $p < .05$) and S⁻/CS⁻ ($F[2,6] = 4.58$, $p < .05$) test conditions. Following treatment with 15 mg/kg of naloxonazine, S⁺/CS⁺ condition-associated responses were

differed in the degree to which they produced nonselective behavioral effects as measured by suppression of responding in the S^-/CS^- condition. With both naltrexone and naltrindole, the attenuation of ethanol-seeking behavior was selective, and lever pressing associated with exposure to the stimuli previously associated with water was not significantly modified. The effect of naloxonazine, on the other hand, was not specific in that the lowest effective dose that attenuated ethanol-seeking behavior also suppressed responses below baseline levels in the S^-/CS^- control condition (Ciccocioppo, Martin-Fardon, & Weiss, 2002).

4.5. Molecular Genetic Manipulations—Knockout of the μ -Opioid Receptor

The creation of new models such as transgenic and null mutant mice using recombinant DNA technology has provided another approach for studying the role of specific receptors in mediating the reinforcing effects of ethanol (Wehner & Bowers, 1995). This approach has particular promise for helping elucidate the mechanism of action for the reinforcing effects of ethanol because ethanol acts on many different neurochemical systems, and vulnerability to alcoholism, it has been hypothesized, results from the influences of many different genes. To address this question in the context of the opioid peptide systems, opioid receptor null mutant mice for the μ , δ , and κ receptors can be tested. To date, studies using animal models for the positive reinforcing effects of ethanol have been conducted with μ - and δ -opioid receptor knockout mice.

In one study, μ -opioid receptor knockout mice were prepared using methods described previously (Matthes, Maldonado, Simonin, Valverde, Slowe, Kitchen, Befort, Dierich, Le Meur, Dollé, Tzavara, Hanoune, Roques, & Kieffer, 1996). These mice were tested for both two-bottle choice ethanol drinking (both before and after operant self-administration training) and operant ethanol self-administration (both nosepoke and lever pressing). In addition, to determine whether there were global differences between knockout and wild-type mice in motivated behavior and/or learning, food-reinforced (see Heyser et al., 1997 for experimental details) and sucrose-reinforced responding were examined. The overall finding in this set of studies was that mice lacking the μ -opioid receptor do not self-administer ethanol. This was true in both operant procedures (Fig. 5), with sweetener added, and in two-bottle choice drinking procedures (Roberts et al., 2000). Wild-type mice consumed approximately 0.6 g/kg ethanol in the 30-minute operant tests and 10–13 g/kg ethanol in the 24-hour bottle drinking tests. In contrast, knockout mice consumed approximately 0.1 g/kg ethanol in the operant tests and 3–5 g/kg ethanol in the bottle drinking tests. Both wild-type and knockout mice self-administered food and

Figure 4. Continued.

significantly reduced by about 55% from 14.63 ± 2.89 (vehicle) to 6.82 ± 2.41 ($p < .05$). However, at this dose, an even greater suppression of behavior was observed in the S^-/CS^- stimulus condition where responding was reduced by 66% from 9.00 ± 1.36 (vehicle) to 3.00 ± 1.10 ($p < .05$) (taken with permission from Ciccocioppo, Martin-Fardon, & Weiss, 2002).

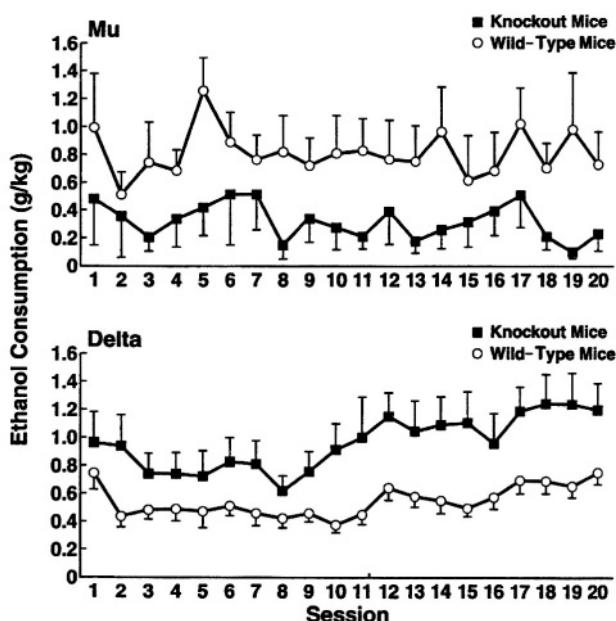


Figure 5. Top: Operant self-administration of 10% ethanol in μ -opioid receptor knockout (squares) and wild-type (circles) mice after a saccharin fading procedure. There was a significant difference between the strains; μ -knockout mice displayed decreased ethanol self-administration relative to wild-type mice (taken with permission from Roberts et al., 2000). Bottom: Operant self-administration of 10% ethanol and water in δ -opioid receptor knockout (squares) and wild-type (circles) mice. δ -Opioid receptor knockout mice displayed greater ethanol preference (data not shown) and increased ethanol consumption relative to wild-type mice. Ethanol consumption is expressed in grams per kilogram of body weight. Values shown are mean \pm SEM (taken with permission from Roberts et al., 2001).

a sucrose solution. Overall, these results support the hypothesis that μ -opioid receptor knockout mice can learn an operant task and will respond for food and a sweet solution, but that they do not respond for ethanol in an operant task and consume only modest amounts in a two-bottle choice situation.

The multiple approaches to examining ethanol consumption that were employed are a major strength of the Roberts et al. (2000) study. Two-bottle choice drinking as the only measure of ethanol's reinforcing capacity potentially is confounded by palatability and lack of information regarding patterns of consumption (Cicero, 1979; Meisch, 1984), and it has been suggested that the operant self-administration technique provides a more reliable test of reinforcement (Meisch, 1984). Several laboratories have successfully developed operant ethanol self-administration procedures using C57BL/6 mice (Risinger, Brown, Doan, & Oakes, 1998; Elmer, Meisch, & George, 1987; Middaugh, Kelley, Cuisin, & Groseclose, 1999). In the above experiments, a two-manipulanda (two holes or two levers), limited-access approach was employed in

which the mice were not deprived of food or water and the ethanol was adulterated only with sweetener during the training phase.

The results presented above suggest that μ -opioid receptors have a critical role in ethanol reinforcement. The exact mechanism by which ethanol modulates μ -receptor function is unclear, though several possibilities have been proposed. Increases in levels of the endogenous opioid **β -endorphin** have been observed following acute and chronic ethanol (Ulm et al., 1995). Also relevant, moderate concentrations of ethanol (25–100 mM) increase the binding capacity of μ -opioid receptors (Charness, 1989). Opioid receptors also may modulate dopamine release (Di Chiara, Acquas, & Tanda, 1996).

4.6. Molecular Genetic Manipulations—Knockout of the δ -Opioid Receptor

Results of studies examining the role of **δ -opioid** receptors in ethanol consumption using pharmacological approaches have been inconsistent. Approximately half of the published articles that used a pharmacological approach in laboratory animals support a role for **δ -opioid** receptors in ethanol drinking (Franck, Lindholm, & Raaschou, 1998; Froehlich, Zweifel, Harts, Lumeng, & Li, 1991; June et al., 1999; Krishnan-Sarin et al., 1995a; Krishnan-Sarin, Portoghesi, Li, & Froehlich, 1995b; Le, Poulos, Quan, & Chow, 1993), whereas the other half support no effect of this receptor subtype in ethanol drinking (Honkanen et al., 1996; Hytytia, 1993; Middaugh, Kelley, Groseclose, & Cuisin, 2000; Stromberg et al., 1998; Williams & Woods, 1998). Although many studies have supported similar actions of μ - and δ -receptors, evidence is beginning to accumulate to suggest that these receptors may work in an opposing manner in certain domains. For example, it recently has been suggested on the basis of the studies with μ - and δ -receptor knockout mice that these receptors may work in an opposing manner to regulate anxiety and mood state (Filliol, Ghozland, Chluba, Martin, Matthes, Simonin, Befort, Gaveriaux-Ruff, Dierich, LeMeur, Valverde, Maldonado, & Kieffer, 2000). μ -Opioid receptor knockout mice have shown evidence of decreased anxiety-like behavior relative to wild-type littermates, whereas δ -receptor knockout mice have shown evidence of increased anxiety-like behavior relative to wild-type littermates in two tests of anxiety, the elevated plus-maze and the light-dark box (Filliol et al., 2000).

Recently, both two-bottle choice ethanol drinking and operant ethanol self-administration were examined in δ -receptor knockout and wild-type mice (Roberts et al., 2001). The generation of δ -opioid receptor knockout mice was described previously (Filliol et al., 2000). The first phase of this study involved 3 days of two-bottle choice testing. Then, mice were group housed and trained in the operant ethanol self-administration procedure described above. At the end of operant testing, mice were singly housed and tested for two-bottle choice ethanol drinking behavior across three 24-hour sessions. Finally, the mice were retested for operant ethanol self-administration, and, immediately following the final session, they were tested in a light-dark transfer procedure to examine anxiety-like responses.

δ -Opioid receptor knockout mice showed no evidence of a preference for ethanol in the first two-bottle choice drinking test; however, after experience with ethanol in the operant self-administration procedure, a preference for ethanol was detected in the second two-bottle choice test. The delayed preference in knockout mice may be related to their increased level of anxiety-like behavior. In the initial two-bottle choice test, both wild-type and knockout mice consumed ethanol levels intermediate to those consumed by C57BL/6J (10 g/kg/day) and 129/J (6 g/kg/day) mice (Belknap, Crabbe, & Young, 1993). This is consistent with the mixed C57BL/6 \times 129 genetic background of these mice. Ethanol consumption of knockout mice increased to approximately 13 g/kg/day in the second phase of two-bottle choice testing, whereas the amount of ethanol consumed by wild-type mice remained fairly constant at approximately 7 g/kg/day. The ethanol intake of knockout mice was equivalent to that observed in the selectively bred high alcohol preferring mice (Grahame, Li, & Lumeng, 1999).

Knockout mice also showed a preference for ethanol over water and self-administered more ethanol than wild-type mice in the operant self-administration paradigm (Fig. 5). Operant responding in wild-type and knockout mice diverged once the ethanol concentration was 8%. Importantly, the ethanol self-administered in this procedure was sufficient to reverse the innate anxiety-like response observed in δ -knockout mice (see below).

This increased ethanol consumption by δ -receptor knockout mice suggests that the δ receptor functions in a manner opposite to the μ receptor and actually may inhibit the reinforcing effects of ethanol. This finding is not consistent with several published studies that suggest that the δ -opioid receptor has a facilitatory role in ethanol reinforcement (Franck et al., 1998; Froehlich et al., 1991; Hyttia and Kiiianmaa, 2001; June et al., 1999; Krishnan-Sarin et al., 1995a,b; Le et al., 1993). However, there are several issues related to the pharmacological approaches commonly used and the potential role of the δ -opioid receptor in anxiety that may help to explain these differences. Pharmacological studies may be compromised by the pharmacokinetics of the antagonists used, a lack of selectivity of the agents available for the δ receptor, or potential partial agonist effects *in vivo* of compounds that act as antagonists *in vitro* (Franck et al., 1998; Takemori & Portoghesi, 1992; Hyttia, 1993; Corbett, Paterson, & Kosterlitz, 1993; Raynor, Kong, Chen, Yasuda, Yu, Bell, & Reisine, 1994; Honkanen et al., 1996; Middaugh et al., 2000; Stromberg et al., 1998; Williams & Woods, 1998; Jackson, Ripley, & Nutt, 1989; Corbett et al., 1993). These factors may be partly responsible for the mixed results that have resulted from investigations of δ -opioid receptor involvement in ethanol consumption that use existing pharmacological approaches.

δ -Opioid receptor knockout mice showed greater anxiety-like response than wild-type mice in the light–dark transfer test (Filliol et al., 2000; Roberts et al., 2001). However, this anxiety-like behavior of knockout mice was attenuated by self-administered ethanol. This is an important finding because it suggests that one role of the δ receptor may be to mediate the interaction between anxiety states and ethanol consumption. In fact, the initial aversion to ethanol by

δ -knockout mice may be related to the increased anxiety-like behavior exhibited by this line. It has been shown that stressor exposure can decrease the consumption of a novel quinine solution (Job & Barnes, 1995). Exposure to ethanol during the saccharin fading procedure may have allowed the mice to become familiar with ethanol and even experience its anxiolytic-like effects. Thus, increased anxiety associated with the lack of the δ receptor may be related to the development of a preference for ethanol in this strain. This potential interaction among the δ -opioid receptor, anxiety state, and ethanol consumption may help to explain the inconsistencies in the literature regarding the role of δ -opioid receptors in ethanol consumption.

5. Summary and Conclusions

Ethanol, like other drugs of abuse, has motivating properties that can be developed as animal models of self-administration. A major strength of the operant approach where an animal must work to obtain ethanol is that it reduces confounds due to palatability and controls for nonspecific malaise-inducing effects. In the domain of opioid peptide systems, limited access paradigms have good predictive validity. In addition, animal models of excessive drinking—either environmentally or genetically induced—also appear sensitive to blockade or inactivation of opioid peptide receptors. Ethanol availability can be predicted by cues associated with positive reinforcement, and these models are sensitive to the administration of opioid antagonists. Perhaps most exciting are the recent results suggesting that the key element in opioid peptide systems that is important for the positive reinforcing effects of ethanol is the μ -opioid receptor. How exactly ethanol modulates μ -receptor function will be a major challenge of future research. Nevertheless, the apparently critical role of the μ receptor in ethanol reinforcement refocuses the neuropharmacology of ethanol reinforcement in the opioid peptide domain and opens a novel avenue for exploring medications for treating alcoholism.

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References

- Belknap, J.K., Crabbe, J.C., & Young, E.R. (1993). Voluntary consumption of ethanol in 15 inbred mouse strains. *Psychopharmacology* 112, 503–510.
- Biggs, T.A., & Myers, R.D. (1998). Naltrexone and amperozide modify chocolate and saccharin drinking in high alcohol-preferring P rats. *Pharmacology Biochemistry and Behavior* 60, 407–413.
- Charness, M.E. (1989). Ethanol and opioid receptor signalling. *Experientia* 45, 418–428.
- Ciccocioppo, R., Angeletti, S., & Weiss, F. (2001). Long-lasting resistance to extinction of response reinstatement induced by ethanol-related stimuli: Role of genetic ethanol preference. *Alcoholism: Clinical and Experimental Research* 25, 1414–1419.

- Ciccocioppo, R., Martin-Fardon, R., & Weiss, F. (2002). Effect of selective blockade of μ_1 or δ opioid receptors on reinstatement of alcohol-seeking behavior by drug-associated stimuli in rats. *Neuropsychopharmacology*, 27, 391–399.
- Cicero, T.J. (1979). A critique of animal analogs of alcoholism. In E. Majchrowicz & E.P. Noble (eds.), *Biochemistry and Pharmacology of Ethanol*, vol. 2. New York: Plenum Press, pp. 533–560.
- Corbett, A.D., Paterson, S.J., & Kosterlitz, H.W. (1993). Selectivity of ligands for opioid receptors. In A. Herz (ed.), *Opioids I* (series title: *Handbook of Experimental Pharmacology*, vol. 104/1). Berlin: Springer-Verlag, pp. 645–673.
- Crabbe, J.C., Phillips, T.J., Cunningham, C.L., & Belknap, J.K. (1992). Genetic determinants of ethanol reinforcement. In P.W. Kalivas & H.H. Samson (eds.), *The Neurobiology of Drug and Alcohol Addiction* (series title: *Annals of the New York Academy of Sciences*, vol. 654). New York: New York Academy of Sciences, pp. 302–310.
- Cunningham, C.L., Fidler, T.L., & Hill, K.G. (2000). Animal models of alcohol's motivational effects. *Alcohol Research and Health* 24, 85–92.
- Di Chiara, G., Acquas, E., & Tanda, G. (1996). Ethanol as a neurochemical surrogate of conventional reinforcers: The dopamine–opioid link. *Alcohol* 13, 13–17.
- Elmer, G.I., Meisch, R.A., & George, F.R. (1986). Oral ethanol reinforced behavior in inbred mice. *Pharmacology Biochemistry and Behavior* 24, 1417–1421.
- Elmer, G.I., Meisch, R.A., & George, F.R. (1987). Differential concentration–response curves for oral ethanol self-administration in C57BL/6J and BALB/cJ mice. *Alcohol* 4, 63–68.
- Filliol, D., Ghozland, S., Chluba, J., Martin, M., Matthes, H.W.D., Simonin, F., Befort, K., Gaveriaux-Ruff, C., Dierich, A., LeMeur, M., Valverde, O., Maldonado, R., & Kieffer, B.L. (2000). Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nature Genetics* 25, 195–200.
- Franck, J., Lindholm, S., & Raaschou, P. (1998). Modulation of volitional ethanol intake in the rat by central delta-opioid receptors. *Alcoholism: Clinical and Experimental Research* 22, 1185–1189.
- Froehlich, J.C. (1995). Genetic factors in alcohol self-administration. *Journal of Clinical Psychiatry* 56 (Suppl. 7), 15–23.
- Froehlich, J.C., Zweifel, M., Harts, J., Lumeng, L., & Li, T.-K. (1991). Importance of delta opioid receptors in maintaining high alcohol drinking. *Psychopharmacology* 103, 467–472.
- Gauvin, D.V., Moore, K.R., & Holloway, F.A. (1993). Do rat strain differences in ethanol consumption reflect differences in ethanol sensitivity or the preparedness to learn? *Alcohol* 10, 37–43.
- Grahame, N.J., Li, T.K., & Lumeng, L. (1999). Selective breeding for high and low alcohol preference in mice. *Behavior Genetics* 29, 47–57.
- Heyser, C.J., Moc, K., Roberts, A.J., & Koob, G.F. (2000). The effects of chronic naltrexone, acamprosate and the combination on the alcohol deprivation effect in rats. *Alcoholism: Clinical and Experimental Research* 24 (5 Suppl.), 14A.
- Heyser, C.J., Schulteis, G., Durbin, P., & Koob, G.F. (1998). Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats. *Neuropsychopharmacology* 18, 125–133.
- Heyser, C.J., Schulteis, G., & Koob, G.F. (1997). Increased ethanol self-administration following a period of imposed ethanol deprivation in rats trained in a limited access paradigm. *Alcoholism: Clinical and Experimental Research* 21, 784–791.
- Honkanen, A., Vilamo, L., Wegelius, K., Sarviharju, M., Hytytia, P., & Korpi, E.R. (1996). Alcohol drinking is reduced by a μ_1 -but not by a δ -opioid receptor antagonist in alcohol-preferring rats. *European Journal of Pharmacology* 304, 7–13.
- Hytytia, P. (1993). Involvement of μ -opioid receptors in alcohol drinking by alcohol-preferring AA rats. *Pharmacology Biochemistry and Behavior* 45, 697–701.
- Hytytia, P., & Kianmaa, K. (2001). Suppression of ethanol responding by centrally administered CTOP and naltrindole in AA and Wistar rats. *Alcoholism: Clinical and Experimental Research* 25, 25–33.
- Hytytia, P., & Sinclair, J.D. (1993). Responding for oral ethanol after naloxone treatment by alcohol-preferring AA rats. *Alcoholism: Clinical and Experimental Research* 17, 631–636.

- Jackson, H.C., Ripley, T.L., & Nutt, D.J. (1989). Exploring delta-receptor function using the selective opioid antagonist naltrindole. *Neuropharmacology* 28, 1427–1430.
- June, H.L., Grey, C., Warren-Reese, C., Durr, L.F., Ricks-Cord, A., Johnson, A., McCane, S., Williams, L.S., Mason, D., Cummings, R., & Lawrence, A. (1998). The opioid receptor antagonist nalmefene reduces responding maintained by ethanol presentation: Preclinical studies in ethanol-preferring and outbred Wistar rats. *Alcoholism: Clinical and Experimental Research* 22, 2174–2185.
- June, H.L., McCane, S.R., Zink, R.W., Portoghesi, P.S., Li, T.K., & Froehlich, J.C. (1999). The delta 2-opioid receptor antagonist naltriben reduces motivated responding for ethanol. *Psychopharmacology* 147, 81–89.
- Katner, S.N., Magalang, J.G., & Weiss, F. (1999). Reinstatement of alcohol-seeking behavior by drug-associated discriminative stimuli after prolonged extinction in the rat. *Neuropsychopharmacology* 20, 471–479.
- Katner, S.N., & Weiss, F. (1999). Ethanol-associated olfactory stimuli reinstate ethanol-seeking behavior after extinction and modify extracellular dopamine levels in the nucleus accumbens. *Alcoholism: Clinical and Experimental Research* 23, 1751–1760.
- Krishnan-Sarin, S., Jing, S.L., Kurtz, D.L., Zweifel, M., Portoghesi, P.S., Li, T.K., & Froehlich, J.C. (1995a). The delta opioid receptor antagonist naltrindole attenuates both alcohol and saccharin intake in rats selectively bred for alcohol preference. *Psychopharmacology* 120, 177–185.
- Krishnan-Sarin, S., Portoghesi, P.S., Li, T.-K., & Froehlich, J.C. (1995b). The delta2-opioid receptor antagonist naltriben selectively attenuates alcohol intake in rats bred for alcohol preference. *Pharmacology Biochemistry and Behavior* 52, 153–159.
- Krishnan-Sarin, S., Wand, G.S., Li, X.W., Portoghesi, P.S., & Froehlich, J.C. (1998). Effect of mu opioid receptor blockade on alcohol intake in rats bred for high alcohol drinking. *Pharmacology Biochemistry and Behavior* 59, 627–635.
- Le, A.D., Poulos, C.X., Quan, B., & Chow, S. (1993). The effects of selective blockade of delta and mu opiate receptors on ethanol consumption by C57BL/6 mice in a restricted access paradigm. *Brain Research* 630, 330–332.
- Li, T.K., Lumeng, L., & Doolittle, D.P. (1993). Selective breeding for alcohol preference and associated responses. *Behavior Genetics* 23, 163–170.
- Ludwig, A.M., & Stark, L.H. (1974). Alcohol craving. *Quarterly Journal of Studies on Alcohol* 35, 899–905.
- Matthes, H.W.D., Maldonado, R., Simonin, F., Valverde, O., Slowe, S., Kitchen, I., Befort, K., Dierich, A., Le Meur, M., Dollé, P., Tzavara, E., Hanoune, J., Roques, B.P., & Kieffer, B.L. (1996). Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the μ -opioid-receptor gene. *Nature* 383, 819–823.
- McBride, W.J., & Li, T.K. (1998). Animal models of alcoholism: Neurobiology of high alcohol-drinking behavior in rodents. *Critical Reviews in Neurobiology* 12, 339–369.
- Meisch, R.A. (1984). Alcohol self-administration by experimental animals. In R.G. Smart, H.D. Cappell, F. B. Glaser, Y. Israel, H. Kalant, W. Schmidt, & E. M. Sellers (eds.), *Research Advances in Alcohol and Drug Problems*, Vol. 8. New York: Plenum Press, pp. 23–45.
- Middaugh, L.D., Kelley, B.M., Cuison, E.R. Jr., & Groseclose, C.H. (1999). Naltrexone effects on ethanol reward and discrimination in C57BL/6 mice. *Alcoholism: Clinical and Experimental Research* 23, 456–464.
- Middaugh, L.D., Kelley, B.M., Groseclose, C.H., & Cuison, E.R. Jr. (2000). Delta-opioid and 5-HT3 receptor antagonist effects on ethanol reward and discrimination in C57BL/6 mice. *Pharmacology Biochemistry and Behavior* 65, 145–154.
- O'Malley, S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., & Rounsvaille, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry* 49, 881–887.
- Rassnick, S., Pulvirenti, L., & Koob, G.F. (1993). SDZ 205,152, a novel dopamine receptor agonist, reduces oral ethanol self-administration in rats. *Alcohol* 10, 127–132.

- Raynor, K., Kong, H., Chen, Y., Yasuda, K., Yu, L., Bell, G.I., & Reisine, T. (1994). Pharmacological characterization of the cloned kappa-, delta-, and mu-opioid receptors. *Molecular Pharmacology* 45, 330–334.
- Reid, L.D., & Hunter, G.A. (1984). Morphine and naloxone modulate intake of ethanol. *Alcohol* 1, 33–37.
- Risinger, F.O., Brown, M.M., Doan, A.M., & Oakes, R.A. (1998). Mouse strain differences in oral operant ethanol reinforcement under continuous access conditions. *Alcoholism: Clinical and Experimental Research* 22, 677–684.
- Robbins, S.J., & Ehrman, R.N. (1992). Designing studies of drug conditioning in humans. *Psychopharmacology* 106, 143–153.
- Roberts, A.J., Gold, L.H., Polis, I., McDonald, J.S., Filliol, D., Kieffer, B.L., & Koob, G.F. (2001). Increased ethanol self-administration in δ -opioid receptor knockout mice. *Alcoholism: Clinical and Experimental Research* 25, 1249–1256.
- Roberts, A.J., Heyser, C.J., & Koob, G.F. (1999). Operant self-administration of sweetened versus unsweetened ethanol: Effects on blood alcohol levels. *Alcoholism: Clinical and Experimental Research* 23, 1151–1157.
- Roberts, A.J., McDonald, J.S., Heyser, C.J., Kieffer, B.L., Matthes, H.W.D., Koob, G.F., & Gold, L.H. (2000). μ -Opioid receptor knockout mice do not self-administer alcohol. *Journal of Pharmacology and Experimental Therapeutics* 293, 1002–1008.
- Rodefer, J.S., Campbell, U.C., Cosgrove, K.P., & Carroll, M.E. (1999). Naltrexone pretreatment decreases the reinforcing effectiveness of ethanol and saccharin but not PCP or food under concurrent progressive-ratio schedules in rhesus monkeys. *Psychopharmacology* 141, 436–446.
- Samson, H.H. (1986). Initiation of ethanol reinforcement using a sucrose-substitution procedure in food- and water-sated rats. *Alcoholism: Clinical and Experimental Research* 10, 436–442.
- Samson, H.H. (1987). Initiation of ethanol-maintained behavior: A comparison of animal models and their implication to human drinking. In T. Thompson, P.B. Dews, & J.E. Barrett (eds.), *Neurobehavioral Pharmacology* (series title: *Advances in Behavioral Pharmacology*, Vol. 6). Hillsdale NJ: Erlbaum, pp. 221–248.
- Sinclair, J.D. (1979). Alcohol-deprivation effect in rats genetically selected for their ethanol preference. *Pharmacology Biochemistry and Behavior* 10, 597–602.
- Sinclair, J.D., & Senter, R.J. (1967). Increased preference for ethanol in rats following alcohol deprivation. *Psychonomic Science* 8, 11–12.
- Sinclair, J.D., & Senter, R.J. (1968). Development of an alcohol-deprivation effect in rats. *Quarterly Journal of Studies on Alcohol* 29, 863–867.
- Spanagel, R., & Holter, S.M. (1999). Long-term alcohol self-administration with repeated alcohol deprivation phases: An animal model of alcoholism? *Alcohol and Alcoholism* 34, 231–243.
- Spanagel, R., Holter, S.M., Allingham, K., Landgraf, R., & Zieglsberger, W. (1996). Acamprosate and alcohol: I. Effects on alcohol intake following alcohol deprivation in the rat. *European Journal of Pharmacology* 305, 39–44.
- Stromberg, M.F., Casale, M., Volpicelli, L., Volpicelli, J.R., & O'Brien, C.P. (1998). A comparison of the effects of the opioid antagonists naltrexone, naltrindole, and β -funaltrexamine on ethanol consumption in the rat. *Alcohol* 15, 281–289.
- Stromberg, M.F., Mackler, S.A., Volpicelli, J.R., & O'Brien, C.P. (2001). Effect of acamprosate and naltrexone, alone or in combination, on ethanol consumption. *Alcohol* 23, 109–116.
- Takemori, A.E., & Portoghese, P.S. (1992). Selective naltrexone-derived opioid receptor antagonists. *Annual Review of Pharmacology and Toxicology* 32, 239–269.
- Ulm, R.R., Volpicelli, J.R., & Volpicelli, L.A. (1995). Opiates and alcohol self-administration in animals. *Journal of Clinical Psychiatry* 56(Suppl. 7), 5–14.
- Veale, W.L. (1973). Ethanol selection in the rat following forced acclimation. *Pharmacology Biochemistry and Behavior* 1, 233–235.
- Volpicelli, J.R., Alterman, A.I., Hayashida, M., & O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49, 876–880.
- Wehner, J.M., & Bowers, B.J. (1995). Use of transgenics, null mutants, and antisense approaches to study ethanol's actions. *Alcoholism: Clinical and Experimental Research* 19, 811–820.

- Weiss, F., Mitchiner, M., Bloom, F.E., & Koob, G.F. (1990). Free-choice responding for ethanol versus water in alcohol preferring (P) and unselected Wistar rats is differentially modified by naloxone, bromocriptine, and methysergide. *Psychopharmacology 101*, 178–186.
- Williams, K.L., & Woods, J.H. (1998). Oral ethanol-reinforced responding in rhesus monkeys: Effects of opioid antagonists selective for the mu-, kappa-, or delta-receptor. *Alcoholism: Clinical and Experimental Research 22*, 1634–1639.

V

Recent Development in Alcoholism: Research on Alcoholism Treatment

Michael J. Eckardt, Section Editor

Overview

Michael J. Eckardt

The six chapters in this section examine selected treatment topics, all of which are of great importance and are written by leaders in the field. Each of these topics is clinically relevant and will become even more so in years to come.

Brown and D'Amico review the treatment of adolescents for alcohol-related problems. The high percentage of high school students that drink five or more drinks on one occasion coupled with the finding that early alcohol use is highly correlated with subsequent alcohol-related problems have resulted in establishing treatment programs for adolescents. Diagnosing alcohol abuse or dependence in adolescents is complicated by comorbidity, use of adult criteria, and failure to take into account developmental issues. In spite of these limitations, instruments are available that have been found valid and reliable.

Relapse rates among adolescents and adults are similar, but predictors of relapse will most likely be different, especially given developmental issues. Some studies indicate successful outcomes associated with being older and in treatment for longer periods of time, whereas increasing severity of psychiatric disorders, especially early-onset conduct disorder, predicted poorer outcomes.

Gomberg reviews treatment for alcohol-related problems in special populations. The question whether one treatment approach fits all is important given the relatively low rates of success. Women are understudied and underrepresented in alcohol treatment programs. Women have more comorbidity, especially depression, and experience more barriers and negative social consequences of treatment for alcoholism. Because the medical consequences accompanying excessive alcohol consumption occur earlier in women and they have fewer financial resources and more family pressure to terminate treatment, there is a compelling need for further research.

Treatment for alcoholism in the elderly is an important area of research, because as the number of elderly increases, the absolute number of individuals consuming excessive amounts of alcohol in this population also increases. It is clear that the diagnostic criteria for alcohol-related problems are not applicable to the elderly. There are some data to suggest that age-specific treatment is better than mixed-age treatment.

Although there are significant differences in the prevalence of alcohol-related consequences among minorities, relatively little research has been conducted.

Cornelius and colleagues review the important treatment topic of alcohol and psychiatric comorbidity. In recent years, it has been documented that a number of psychiatric disorders are present in alcoholics, and significant associations are reported for affective disorders, anxiety disorders, drug use disorders, and even for schizophrenia. Although the presence of a psychiatric disorder in alcoholics is predictive of an increased likelihood of relapse, relatively little research has been conducted. There are some data to suggest that serotonin reuptake blockers and tricyclics are useful for treating alcoholics with depression, and buspirone has utility in treating alcoholics with anxiety disorders. In spite of these promising findings, there are relatively few alcohol and psychiatric comorbidity studies.

Hurt and Patten review the treatment of tobacco dependence in alcoholics. Smoking in alcoholics is two to three times more prevalent than that in the general population, and there has been little change in the past 30 years. Moreover, alcoholic smokers are more dependent on nicotine than nonalcoholics and often continue to smoke, even though they stop drinking alcohol. Acceptance of treatment for tobacco dependence in an alcoholism treatment program has been difficult, in part, because alcoholics are less successful in stopping smoking. This is particularly distressing when data suggest that there are minimal risks associated with treatment for tobacco dependence in alcoholics, whereas there is increased risk of morbidity and mortality in tobacco-associated diseases in previously treated alcoholics.

Pharmacological treatment is an important component of treating tobacco dependence, so efficacy should be examined in alcoholic smokers, especially when combined with behavioral therapy. First-line medications include nicotine gum, nicotine patches, nicotine nasal spray, nicotine vapor inhaler, and bupropion, and second-line medications include nortriptyline and clonidine.

Fleming provides an update on the literature related to brief interventions for treating alcohol-related problems. Brief intervention/brief counseling is designed to reduce alcohol consumption in non-treatment-seeking individuals. A physician or nurse usually administers the intervention for 5–10 minutes, one to three times during a 6–8 week period. It consists of assessment, feedback, goal setting, behavior modification, self-help bibliography, and follow-up reinforcement.

Brief interventions, it has been shown, reduces alcohol consumption, health care use and costs, mortality and morbidity, and are equally effective for

men, for women, and for all age groups older than 18. It is unfortunate that the effects on individuals who satisfy criteria for alcohol dependence are not yet known. It would be of great value to know what characterizes those 30–40% that responds favorably to the brief intervention.

Miller reviews the literature on spirituality, treatment, and recovery. Spirituality is not the same as religion, although they overlap conceptually. Spirituality is often considered a protective factor in risk of alcoholism.

Within Alcoholics Anonymous (AA), spirituality is also considered of critical importance to recovery. AA does not claim to be a religion or treatment but provides a spiritual program embodied in its 12 steps. Self-motivated attendance at AA meetings has been found associated with recovery. There have been treatment methods based on the AA program designed to get alcoholics involved in AA. These 12-step programs have been as effective as other behavioral treatment programs.

There are other approaches to spirituality and treatment for alcohol-related disorders. Enhanced affiliation with a disciplined religious community and meditation are examples.

Outcomes of Alcohol Treatment for Adolescents

Sandra A. Brown and Elizabeth J. D'Amico

Abstract. Alcohol and other drug use by youth continue to be an important focus for this nation. Both moderate and heavy alcohol consumption are associated with a higher risk of alcohol-related medical consequences and accidental injuries for youth. Despite knowledge of possible consequences, a high percentage (30%) of high school students nationwide reports episodes of hazardous drinking (five or more drinks on one occasion). Increased awareness and concern related to adolescent substance use has led to the outgrowth of additional treatment facilities and programs for this age group. This chapter examines the impact of developmental factors on the assessment process and subsequent treatment of adolescent alcohol use disorders. In addition, treatment outcome research, intervention studies, relapse, and factors that may influence the recovery process of youth are discussed.

1. Prevalence

Adolescent and young adult alcohol use continues to be a tremendous problem for this nation (Center for Disease Control and Prevention (CDCP), 1998; Johnston, O'Malley, & Bachman, 2000). Surveys indicate that the use of alcohol among adolescents remains high, for example, 50% of twelfth grade high school students report alcohol use in the last 30 days (Johnston et al., 2000). Hazardous drinking (e.g., five or more drinks on one occasion) also continues to be a frequent occurrence, with more than 30% of all adolescents nationwide reporting episodes of binge drinking (CDCP, 1998).

Both moderate and heavy alcohol consumption are associated with a higher risk of alcohol-related accidental injuries and medical consequences (Cherpitel, Tam, Lorraine, Caetano, & Greenfield, 1995; Chou, Grant, & Dawson, 1998). The most common problems that adolescents report experiencing due to drinking

are behavior they later regretted (52%) and inability to think clearly because of their alcohol use (30%) (O'Malley, Johnston, & Bachman, 1998). The frequency of these types of consequences is strongly associated with the age at which youth begin drinking (Chou & Pickering, 1992). A younger age of initiating alcohol use is also highly correlated with alcohol misuse at ages 17–18 (DeWit, Offord, & Wong, 1997) and a higher risk of progression to either alcohol abuse or dependence later in life (Lewinsohn, Rohde, & Seeley, 1996; Nelson & Wittchen, 1998).

Nearly one-third of high school students (31%) report that they have consumed alcohol before 13 years of age (CDCP, 1998), so many youth may be at risk for developing future problems related to alcohol. One study of a community sample of adolescents found that youth who reported problem drinking were more likely to experience elevated rates of alcohol and substance use disorders in young adulthood compared to youth who reported nonproblematic use of alcohol (Rohde, Lewinsohn, Kahler, Seeley, & Brown, 2001).

Longitudinal data from general population studies have shown that adolescents who drink typically begin experimenting with beer or wine, followed by hard liquor or cigarettes. For most adolescents, the risk period for the first drink of alcohol begins at age 11 and peaks at ages 16 and 18. The risk period for onset of regular alcohol use begins around age 14 and peaks at age 19 (DeWit et al., 1997). If other drug use occurs, marijuana use follows alcohol use, which is then followed by other illicit drug use (Kandel & Faust, 1975; Kandel, Yamaguchi, & Chen, 1992). This sequence of use is similar across different ethnic groups (Ellickson, Hays, & Bell, 1992). Of note, adolescents who report binge drinking or who escalate their alcohol use during an academic year also report earlier onset and regular use of cigarettes and earlier onset of marijuana use than those youth who drink without bingeing or those who decrease their alcohol use during an academic year (D'Amico et al., in press).

Martin and his colleagues (Martin et al., 1996a) described a similar progression of use pattern for adolescents diagnosed with alcohol abuse. Most of the youth being treated were also polydrug users and reported a consistent pattern in the age of onset of their substance use: alcohol, followed by marijuana, followed by other drugs (Martin et al., 1996a; Martin, Kaczynski, Maisto, & Tarter, 1996b).

In one of the few cohort-sequential studies, Chen and Kandel (1995) examined the natural history of the use of different substances in a general population by following up a cohort of adolescents first contacted in 1971 at three different times (1980, 1984, and 1990). Results from this 19-year period indicated that of all of the drugs people reported using, alcohol and cigarettes showed the most persistence of use, followed by marijuana.

2. Assessment and Diagnosis

Increased awareness and concern related to adolescent alcohol and drug use has led to the outgrowth of additional treatment facilities and programs for

this age group (Myers, Brown, & Vik, 1998). *The Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) (American Psychiatric Association, 1994) is typically used to assess alcohol and other drug abuse and dependence in this population, however, these criteria were developed for the adult population and therefore tend to fall short in diagnosing adolescents (Brown, 1999; Martin, Kaczynski, Maisto, Bukstein, & Moss, 1995; Winters, 1999). For example, in the DSM-IV field trials, only one of the seven research sites provided data from an adolescent population (Cottler et al., 1995). Bukstein and Kaminer (1994) report that there is little empirical support or conceptual evidence for describing substance diagnoses for adolescents in terms of adult disorder. They outline several problems with the current classification system: the adult diagnostic system has not been established as applicable to an adolescent population, the diagnostic system currently defines a population that is too heterogeneous, and an abuse or dependence diagnosis in adolescence may be debatable due to the possibility of concurring factors such as another psychiatric disorder or dysfunction in the family setting. A recent paper by Meyer and colleagues provides an integrated overview of the theoretical, research, and clinical issues that may impact adolescent substance use assessment, such as comorbidity, the time frame of the assessment, and sources of collateral information (Meyers et al., 1999).

Martin and colleagues empirically examined several of these issues and found that adolescents who abuse substances do tend to show excessive heterogeneity in abuse symptoms (Martin et al., 1995). In addition, the presentation of tolerance, withdrawal, and medical problems is different in adolescents from that found in adults. For adolescents, tolerance is less specific in its relation to the diagnosis of alcohol, and withdrawal symptomatology is much lower in this age group compared with adults (Martin et al., 1995). Of note, Brown and colleagues reported that a different pattern of withdrawal symptoms is evident among adolescents compared to adults and these symptoms may be more predictive of long-term neurocognitive deficits relative to other indexes of drinking (Stewart & Brown, 1995; Tapert & Brown, 1999). It appears, therefore, that the specific developmental needs of adolescents may create special issues in assessing alcohol abuse and dependence in this age group (Brown, 1999; Winters, 1999).

Recent examination of the accuracy of DSM-IV criteria for the progression of alcohol abuse and dependence in an adolescent population indicates more clearly how development may influence this diagnosis (Martin, Langenbucher, Kaczynski, & Chung, 1996c). Martin and colleagues (Martin et al., 1996c) assessed youth with a range of drinking practices and severity; half of the participants was recruited from inpatient and outpatient programs and half from community advertisements. Results indicated that among these adolescents, abuse symptoms did not consistently precede dependence symptoms. In all cases, withdrawal occurred after other abuse and other dependence symptoms. Similarly, in a 5-year prospective study of adolescents and young adults, Nelson and Wittchen found that youth with alcohol problems reported the symptoms, using in greater amounts than intended and spending a lot of time

recovering from use, much more frequently than withdrawal or physical or psychological consequences (Nelson & Wittchen, 1998). Further, in a sample of high school youth, the dependence criterion, giving up activities to use substances, was the most predictive of a diagnosis of dependence in this population (Harrison, Fulkerson, & Beebe, 1998). Emergence of particular dependence symptoms before abuse symptoms is therefore not uncommon (Pollock & Martin, 1999). Thus, developmentally the negative reinforcing "relief" drinking to avoid withdrawal may not be as important in diagnosing adolescent dependence; instead, the contribution of the positively reinforcing effects of alcohol appear more paramount (Martin et al., 1996c).

The difficulty of diagnosing alcohol abuse and dependence in adolescents is often further complicated by the existence of co-occurring psychiatric disorders. Youth who have substance use disorders are at increased risk of a variety of psychopathologies (Wilens, Biederman, Abrantes, & Spencer, 1997). In a recent study of 98 adolescents diagnosed with a substance use disorder, Mikulich and colleagues found that 79% of the youth met criteria for conduct disorder diagnoses, 7% for an anxiety disorder, 16% for attention deficit hyperactivity disorder, 12% for depression, 16% for oppositional defiant disorder, and 6% for posttraumatic stress disorder (Mikulich, Hall, Whitmore, & Crowley, 2001). Overall, lifetime prevalence for affective disorders and conduct disorder tend to be much higher in an adolescent population compared with an adult population (61% and 81%, respectively, versus 41% and 35% in adults) (Deas, Riggs, Langenbucher, Goldman, & Brown, 2000), which highlights the difficulty of diagnosing and treating alcohol abuse or dependence in this population.

In sum, several of the limitations of using DSM-IV criteria (American Psychiatric Association, 1994) in diagnosing adolescent alcohol abuse and dependence are that specific developmental issues may not be taken into account, heterogeneity exists due to the one-symptom threshold for an abuse diagnosis, abuse symptoms may not always precede dependence symptoms, a high percentage of regular users may display one or two dependence symptoms but no abuse symptoms, and impairment may be difficult to assess because it may be a function of another psychiatric disorder or family dysfunction (Brown, Tate, Vik, Haas, & Aarons, 1999; Bukstein, Brent, & Kaminer, 1989; Martin et al., 1995; Winters, 1999).

During the past decade, interviews and measures have been developed to address this problem so that alcohol abuse and dependence can be more accurately assessed in this age group. On a broad level, these structured interviews are used to assess both alcohol and drug use and other psychiatric disorders. The most commonly used interviews are the Diagnostic Interview Schedule for Children (DISC), the Kiddie SADS (K-SADS), the Diagnostic Interview for Children and Adolescents (DICA), and the Structured Clinical Interview for DSM (SCID), typically used with older adolescents.

The most recent DISC is based on the DSM-IV criteria (Shaffer, Fischer, & Dulcan, 1996); however, it has shown only modest reliability for DSM-III-R substance use disorders (Roberts, Solovitz, Chen, & Casat, 1996). The K-SADS

is a youth version of the schedule for affective disorders and schizophrenia. Martin and Winters (1998) report that currently, there are no reliability and validity studies for alcohol and drug use disorders for the new DSM-IV version of the K-SADS (K-SADS-E-5), so one should use caution when using this measure. It has been shown that the DICA, which now incorporates DSM-IV criteria (Reich, Shayla, & Taibelson, 1992), is reliable and valid (Martin & Winters, 1998). The SCID was modified by Martin and colleagues to assess substance use disorders in adolescents, and good concurrent validity was shown (Martin et al., 1995). They also found high interrater reliability on the SCID for individual DSM IV alcohol symptoms ($\kappa = .84\text{--}1.0$) and alcohol diagnoses ($\kappa = .94$) and a good level of agreement for symptom ratings, diagnostic assignments, and age of onset for symptoms when two independent raters observed the same SCID interview (Martin, Pollock, Bukstein, & Lynch, 2000).

Psychometrically evaluated structured interviews have also been developed that specifically focus on alcohol and drug use disorders in this population (Brown et al., 1998; Cottier, Robins, & Helzer, 1989; Winters, Stinchfield, Fulkerson, & Henly, 1993). The Adolescent Diagnostic Interview (ADI) assesses sociodemographic information, alcohol and drug use history, psychosocial functioning, and the symptoms of alcohol and other drug use disorders, as defined in DSM-III-R and DSM-IV. The ADI has shown good reliability and validity (Winters et al., 1993). The Customary Drinking and Drug Use Record examines both lifetime and current alcohol and drug use and problems, DSM-III-R and DSM-IV symptoms, and age of onset for these behaviors. The instrument was found internally consistent and had high test-retest reliability coefficients. In addition, the measure had good convergent, discriminant, and criterion validity (Brown et al., 1998). Finally, the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) measures DSM-III, DSM-III-R, Feighner, RDC, and ICD-10 diagnoses for alcohol, tobacco, and nine classes of psychoactive drugs. It has shown high reliability for both DSM-III and III-R diagnoses (Cottier et al., 1989) and high test-retest reliability (Compton, Cottler, Dorsey, Spitznagel, & Mager, 1996).

In sum, DSM-IV criteria may have several limitations when applied to an adolescent population. There are new options available, however, and many of the recent instruments are specifically tailored to adolescents and have shown good reliability and validity in diagnosing adolescent substance use disorders (Brown et al., 1998; Cottier et al., 1989; Winters et al., 1993).

3. Treatment Outcome Research

Treatment outcome research for alcohol use disorders in adolescents has lagged behind adult substance outcome research (Brown, 1999). For example, one review examined findings for the efficacy of 211 alcohol treatment programs, and only two of the studies had a mean age below 21 years (Miller et al., 1995). Although there is a great deal of work written on approaches to treatment

for adolescents and the possible factors that may contribute to alcohol involvement, there is limited empirical data on adolescents who receive treatment and on long-term outcomes following treatment (Brown, 1999; Winters, 1999).

Adolescence is a period marked by considerable biological, cognitive, and social changes, all of which may influence functioning. The pubertal changes that take place during adolescence are strongly linked with a variety of social, relational, emotional, and cognitive factors (Brooks-Gunn, Graber, & Paikoff, 1994), which can play a large role in initiating and maintaining alcohol consumption (Tschan et al., 1994). As with the assessment of alcohol and other drug disorders, treatment of these disorders must therefore factor in the special needs of this population.

As shown in Figs. 1 and 2, the rates of return to alcohol or drug use are relatively comparable to those of adults who receive treatment for alcohol or other drug problems (Brown, 1999); however, different factors may motivate adolescents' initial alcohol use, maintenance of use, and potential relapse. Brown and colleagues (Brown, Vik, & Creamer, 1989) found, for example, that the vast majority of adolescents, who had been in treatment for alcohol and drug problems and relapsed, reported social factors as the most frequent reason for their relapse (e.g., pressure to use in a social situation). A more recent investigation supported this finding; 59 youth with alcohol and drug disorders reported social pressure, withdrawal, and negative affect among the most frequent reasons for relapsing (Cornelius et al., in press). This environmental context of relapse is very different from reports of adult relapse in which negative emotional states and interpersonal conflict have been identified as the most prevalent reasons for addiction relapse (Marlatt & Gordon, 1980). Second,

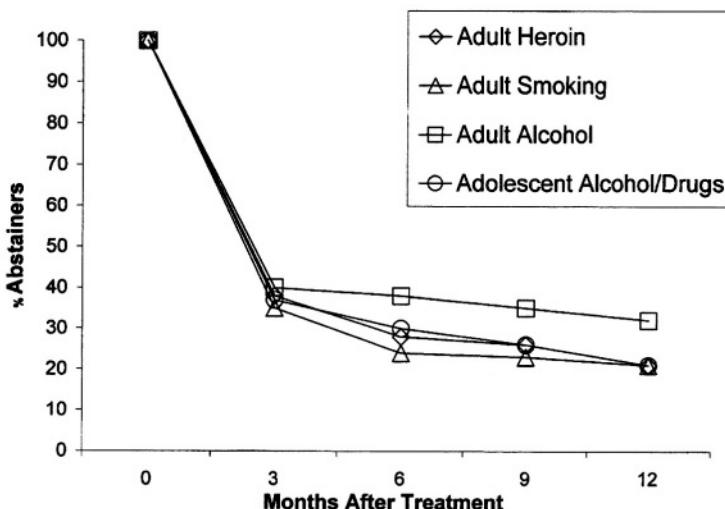


Figure 1. Survival rates: adults and adolescents. Note: adult relapse from Hunt, Barnett, and Branch, 1971.

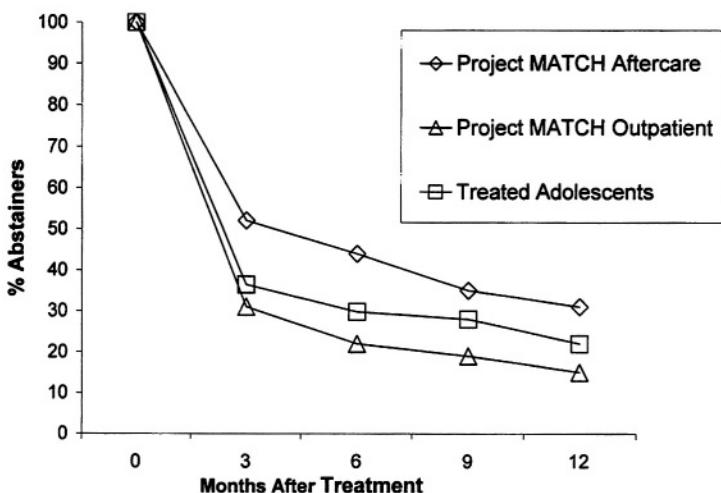


Figure 2. Survival rates: Project MATCH and treated adolescents. Note: Project MATCH data: *Journal of Studies on Alcohol*, 1997.

adolescents who present for treatment typically use multiple substances, which is associated with a poorer outcome in the adult literature (Brown, Mott, & Myers, 1990; Brown et al., 1989). Teens also tend to have a shorter duration of substance involvement than adults who enter treatment; therefore, the presentation of symptoms and the adverse consequences that are seen in this population are different from those evident among adult clinical populations (Brown, 1993; Martin et al., 1995). Finally, the stressors that adolescents experience vary depending on age and social and emotional stage of development (Brown, 1993). All of these factors can contribute to an adolescent's successful treatment outcome and should therefore be considered when developing treatment programs.

Available treatment outcome research for this population has focused on: (1) pretreatment characteristics that may predict outcome, (2) posttreatment clinical course, and more recently, (3) treatment process (Brown, 1999). Previous studies that have attempted to evaluate treatment efficacy were largely descriptive and were conducted when there were few programs available that specifically addressed adolescents' needs (e.g., Hubbard, Cavanaugh, Graddock, & Rachel, 1983; Rush, 1979; Sells & Simpson, 1979); thus, there is limited generalizability of these findings (Brown, 1999).

Typically, successful treatment outcomes for adolescents are associated with length of time in treatment (Hser et al., 2001) and being older, whereas poorer outcome is related to more severe psychiatric symptoms and early onset of conduct disorder (Brown, 1999). Friedman et al. examined 33 demographic and substance use characteristics that might predict outcome for both an inpatient and outpatient adolescent population (Friedman, Terras, & Ali, 1998). Results indicated that younger age, more education, not having dropped out of high school, not having been expelled from school, not being Catholic, and not

being court referred to treatment were all associated with a greater decrease in substance use for the inpatient sample. For the outpatient sample, being female, not having been expelled from school, a high level job for the client's head of the household, and being self-referred all predicted a better outcome. A more recent study found that the most predictive factor for a favorable outcome for adolescents was length of treatment, even when patient problem severity was statistically controlled (Hser et al., 2001). Additional work in this area is needed to further explore pretreatment characteristics and their association with treatment outcome.

4. Intervention Studies

4.1. *Self-Help Programs*

Self-help groups for alcohol typically include the 12-step programs that focus on anonymity. Most adolescent treatment programs (90%) currently include Alcoholics Anonymous (AA) as a component of their treatment (Brown, 1999). There is evidence that AA group attendance is related to high levels of commitment to abstinence and improved substance use outcomes for adults (Morgenstern, Labouvie, McCrady, Kahler, & Frey, 1997) and also for youth (Brown, 1993).

In one study, Brown found that 57% of adolescents who received inpatient treatment for alcohol abuse or dependence reported that they attended 12-step meetings regularly during the year following treatment. Of these youth, 69% had positive alcohol outcomes during the first year after treatment. In contrast, only 31% of those who did not attend meetings regularly (e.g., 0–10 sessions during the year after treatment) had positive outcomes (Brown, 1993). In a more recent study, Kelly et al. (2000) reported that adolescents who attended 12-step meetings in the first 3 months after treatment showed enhanced motivation for abstinence and meeting attendance was related to continued abstinence as well as to reductions in substance use behavior. For adolescents, 12-step group attendance appears to influence positive treatment outcomes by enhancing factors critical for self-regulation, such as motivation for abstinence and use of abstinence focused coping strategies, rather than immediately improving self-efficacy for alcohol-related situations (Kelly et al., 2000).

Because the 12-step programs were originally developed for an adult population, the specific developmental needs of adolescents may not be addressed (Brown, 1999). Further research examining the possible benefits of this approach for youth and the role of emotional and cognitive development in the efficacy of 12-step programs is merited.

4.2. *Systems Oriented Interventions*

Family oriented approaches to adolescent alcohol and drug abuse have become more prevalent during the last decade, thus providing more opportunity

to study the efficacy of this treatment (Liddle & Dakof, 1995). Liddle and Dakof (1995) provide a comprehensive review of the historical context of family-based treatment and the current empirical support for this treatment. Much of the early family-based work focused on problem behaviors (e.g., conduct disorder). Although these strategies did not focus on substance use, they had a positive impact on problem behavior overall, thus paving the way for testing the efficacy of these techniques specifically for substance abuse (Liddle & Dakof, 1995).

Subsequently, researchers have examined the potential benefits of family therapy for treating adolescent substance use. Specifically, Szapocznik et al. (Szapocznik, Kurtines, Foote, Perez-Vidal, & Hervis, 1986; Szapocznik, Kurtines, & Hervis, 1983) examined two family-based approaches, conjoint family therapy (all family members present), and one-person family therapy (at least one family member present for most sessions). Both approaches reduced substance use and problem behaviors in Hispanic adolescents at 6- and 12-month follow-ups. In addition, family functioning improved overall (Szapocznik et al., 1983, 1986).

Although these first studies focused on polydrug use with small samples and there were no comparison groups, findings suggested that this approach could be used successfully to reduce substance use in this age group (Szapocznik et al., 1983). It is not entirely clear, however, whether other forms of adolescent treatment (e.g., peer or individual) would have been as effective as family-based treatment in decreasing alcohol and drug related problems (Liddle & Dakof, 1995).

Research has begun to answer this question by assessing the efficacy of family treatment compared with other available treatments (Henggeler, Melton, & Smith, 1992; Joanning, Quinn, Thomas, & Mullen, 1992; Lewis, Piercy, Sprenkle, & Trepper, 1990). Specifically, youth who participated in family-based treatment reported less drug use at the end of treatment than those who received peer group therapy (Joanning et al., 1992) or parent education (Joanning et al., 1992; Lewis et al., 1990).

Like the family-based approaches discussed above, Multisystemic Therapy (MST) is also based on treating the family system, although MST is more intensive (e.g., several hours of treatment per week vs. 50 minutes) and also focuses on factors in the social networks of adolescents and families that are related to subsequent antisocial behavior (Henggeler, 1998). MST has been examined in relation to typical community training (Henggeler et al., 1986), parent training (Brunk, Henggeler, & Whelan, 1987), and outpatient counseling (Borduin, Henggeler, Blaske, & Stein, 1990). MST showed greater improvements in family relations (Henggeler et al., 1986), problematic parent-child relations (Brunk et al., 1987), and a greater reduction in recidivism for both sexual offenses and criminal offenses (Borduin et al., 1990), compared to these other available treatments. MST has also been found to reduce reports of a combined index of alcohol and marijuana use posttreatment (Henggeler et al., 1992) and has recently been adapted with a community reinforcement approach to more effectively detect and address adolescent substance abuse (Randall, Henggeler, Cunningham, Rowland, & Swenson, 2001).

4.3. Brief Interventions

Recent efforts in brief intervention have shown promise in reducing adolescent drinking and consequences experienced from drinking (Breslin, Sdao-Jarvie, & Pearlman, 1998; Marlatt et al., 1998; Monti et al., 1999). These brief interventions have been implemented in several different settings, such as primary care (Breslin et al., 1998), an emergency room (Monti et al., 1999), and high school settings (Brown, 2001; D'Amico & Fromme, 2002), indicating the flexibility of such an approach.

Monti and his colleagues have shown that a motivational, brief alcohol intervention given to older adolescents (e.g., 18–19 year olds) in an emergency room setting was sufficient to decrease reports of drinking and driving and alcohol-related problems. Breslin also recently developed a brief cognitive behavioral outpatient intervention for youth that is designed to motivate behavioral change related to substance use (Breslin et al., 1998). Both of these programs indicated that age-related factors were significantly related to the efficacy of the intervention, thus supporting the notion that developmental factors should be considered when intervening with this age group.

Brief interventions have also recently been implemented in high school settings. D'Amico and Fromme conducted a brief group intervention with adolescents in a high school setting that targeted several risk-taking behaviors. Youth who participated in the 50-minute Risk Skills Training Program (RSTP) reported significant decreases in drinking, driving after drinking, and riding with a drunk driver at a posttest assessment, compared to a control group and to adolescents who received an educational intervention (D'Amico & Fromme, 2002). Brown implemented a voluntary self-selection intervention in a high school setting where students could choose to get information related to alcohol use in a group or individual setting or on a website. Preliminary results indicate that the intervention may alter perceptions of peer use and delay progression to heavier alcohol use (Brown, 2001).

4.4. Cognitive and Behavioral Therapy

Studies that evaluated the efficacy of behavioral treatment for substance abuse are limited; however, more recent research efforts are targeting this area. Findings have shown improvements among substance abusing adolescents who received this type of treatment, compared with standard counseling (Azrin, Acierno, Kogan, & Donohue, 1996). Components included in one behavioral treatment were (1) stimulus control, (2) an urge-control procedure, and (3) behavioral contracting. Participants who completed the behavioral treatment decreased their drug use by 63% at a posttest and by 73% at a 1 month follow-up, whereas supportive counseling participants did not decrease their drug use at either time. Thus, there is initial support for this type of treatment with an adolescent age group (Azrin et al., 1996). Other research has compared the efficacy of cognitive behavioral therapy (CBT) to interactional

therapy (IT) among dually diagnosed adolescent substance abusers. Results indicated that youth who participated in the CBT group reported less severe substance use at a 3-month follow-up, compared to adolescents in the IT group. Positive trends were also found for the CBT group for family functioning, peer-social relationships, legal problems, and psychiatric problems, compared to the IT group (Kaminer, Burleson, Blitz, Sussman, & Rounsville, 1998).

More recent models have begun to include both behavioral strategies and family therapy to treat adolescent substance abuse because this approach may provide better outcomes than either individual approach (Waldron, Brody, & Slesnick, 2001a). Individual sessions with the adolescent focus on coping, decision making, emotion regulation, and other interpersonal factors that may contribute to use. Family therapy sessions are also based on a behavioral systems approach and the goal is to improve relationships (Waldron et al., 2001a). A randomized clinical trial of 114 families of adolescents referred for substance use treatment compared outcomes for stand-alone family therapy, individual cognitive behavioral therapy, combined individual and family therapy, and a group intervention (Waldron, Slesnick, Brody, & Peterson, 2001b). Results at a 4-month follow-up indicated that youth in the family therapy alone and the combined interventions reported significantly fewer days of substance use. At a 7-month follow-up, the combined and group intervention youth reported fewer days of use, and changes in use levels were found for the family, combined, and group interventions (Waldron et al., 2001b). Further research is needed in this area to determine the long-term effects of behavioral therapy and to better understand the impact of integrating family therapy and individual behavioral therapy for this population.

4.5. *Pharmacotherapy*

The use of pharmacotherapy treatment for adolescents with an alcohol disorder is limited (Brown, 1999), which may be a result of developmental risks, social stigma, and issues related to long-term effectiveness (Kaminer, 1995). Some of the pharmacotherapeutic strategies that have been used include craving reduction, substitution therapy, aversive therapy, and treatment of underlying psychiatric conditions (Solkhah & Wilens, 1998). Solkhah and Wilens recently reviewed the published research and found only 10 studies (two controlled studies, four open trials, and four case reports) that assessed the effects of medication for treating alcohol or substance abusing youth. The studies differed in their methods and definition and measurement of treatment outcome. Results also varied from study to study. Solkhah and Wilens suggested the need for more controlled studies to evaluate the possible effects of medication for alcohol abusing adolescents (Solkhah & Wilens, 1998).

One of the first studies to examine the impact of SSRI medication in adolescents with an alcohol use disorder was recently conducted by Cornelius and colleagues (Cornelius et al., 2001). They evaluated the efficacy of fluoxetine for treating adolescents with current comorbid major depression and an alcohol

use disorder and found significant decreases in both depression and frequency and quantity of drinking after 12 weeks. The authors acknowledge that the study was limited, however, as the design did not include a placebo group and was not double blind (Cornelius et al., 2001).

Finally, compliance with medication is an important issue for this population because developmental stage, co-occurrence of other psychiatric disorders, and the family environment may all substantially influence the level of compliance. One study found that 25% of alcohol abusing adolescents were noncompliant with taking their medication and an additional 8% had either abused the medication or made it available to others for illicit use (Wilens, Biederman, Abrantes, & Spencer, 1996). Adolescents with a substance use disorder are at increased risk for dysfunction in a number of domains (Wilens et al., 1997), so the issues of compliance and possible medication interactions are of great concern (Brown, 1999). Future research should begin to examine ways to facilitate compliance by addressing the specific developmental factors that impact this age group.

4.6. Self-Change Efforts

Many adolescents and adults who have had problems with alcohol do not resolve these problems through formal treatment but instead appear to resolve alcohol problems without treatment (Wagner, Brown, Monti, Myers, & Waldron, 1999). In one prospective study, a high-risk sample of adolescents (ages 13–18) was followed for six years. Of these youth, approximately half developed alcohol abuse, and half were able to resolve excessive drinking and alcohol-related problems for at least a 2-year period without receiving any type of formal treatment (Wagner et al., 1999). As adolescents transition to new behavioral or interpersonal stages, their drinking may change, and a "maturing out" effect may take place as they progress into young adulthood and experience associated changes in work or family activities (Donovan & Jessor, 1985).

Recent longitudinal research in this area has supported previous findings and shown that many youth make efforts to decrease high-risk drinking. For example, Stice and colleagues conducted a prospective study of adolescent drinking and found that a portion of adolescents (14%) decreased their drinking during the 9-month school year without any formal treatment (Stice, Myers, & Brown, 1998). D'Amico and colleagues assessed 621 high school student drinkers during an academic year and found four different drinking trajectories: 35% of adolescents reported nonproblem drinking, 35% reported binge drinking (five or more drinks on two or more occasions in the past month), 14% increased from drinking to binge drinking, and 16% transitioned out of binge drinking to either moderate drinking or abstinence (D'Amico et al., 2001). Results suggested that youth with lower levels of perceived student drinking were less likely to escalate their use of alcohol during the year. Thus, decreased perceptions of peer use appeared to be a protective factor for onset of binge drinking (D'Amico et al., 2001). Examination of the personal change

process for adolescents is critical to understanding the progression and remission of youth substance involvement during this period of rapid transition.

5. Outcome Process Research for Adolescence

As noted above, there are significant concerns regarding the generalizability of adult-based research findings to alcohol abusing adolescents. This is particularly the case in investigations of the process or mechanisms that influence maintenance of behavioral change (e.g., abstinence) or relapse following treatment of adolescents (Stice et al., 1998). In addition to potential differences in behavioral outcomes of alcohol treatment (i.e., alcohol use, quality of life, functioning on major life domains), developmental factors may directly influence or moderate the processes whereby behavioral change is maintained or a return to alcohol use unfolds.

5.1. *Developmental Factors and Family Context*

Recent developments in studying adolescent alcohol treatment outcome highlight the potential role of several developmental factors in the outcome process. Neuroanatomical maturation continues into adolescence, including changes in cerebral metabolic rates (Harris, 1995), alterations in redundancy of synaptic connections (Huttenlocher, 1990), and myelination of frontal and parietal association areas (Kolb & Fantie, 1997). The neurocognitive consequences of these changes have important implications for attention, risk appraisal, and coping skills, all of which influence alcohol use decisions for adolescents (Myers & Brown, 1990). Several aspects of social development such as increased priority of peer relations and exposure to new interpersonal situations alter the likelihood of exposure to alcohol in the immediate environment. In addition, role transitions, which occur rapidly during adolescence (e.g., joining the work force, independent living, obtaining a driver's license), significantly affect the potential adverse consequences of adolescent use of alcohol. Finally, other problems that commonly emerge during adolescence (e.g., delinquency, depression) may alter the nature of both risks and resources available to youth before, during, and after treatment. Thus, developmental changes during adolescence may influence both the process and outcome following treatment for alcohol problems.

In addition to developmental stage differences between adolescents and adults who receive treatment for alcohol problems, the family context of youth can influence access and barriers to treatment, the likelihood of retention and involvement in treatment, and posttreatment resources and risks. For example, treatment drop-out rates are elevated for youth (Winters, 1999), and retention of families in treatment has been found to be a key factor in success for youth with alcohol, drug, and conduct disorder problems (e.g., Lewis et al., 1990). Further, pretreatment family characteristics impact both the

adaptational demands of adolescents after treatment and the outcome of youth who receive inpatient treatment for alcohol problems (Stewart & Brown, 1994; Vik, Grizzle, & Brown, 1992).

5.2. Heterogeneity of the Adolescent Treatment Population

The existing literature on theoretically based process investigations of adolescent alcohol treatment outcome is limited. However, a number of factors have been identified that may be critical to understanding sustained resolution as well as the resurgence of alcohol involvement for youth. One such area is the heterogeneity of youth who need or receive treatment. Recent studies indicate that up to one-third of high school students wish that they could reduce their alcohol consumption and approximately one in seven have made personal attempts to stop; yet, only half of those who felt the need for treatment for their alcohol problems actually received treatment (Smart & Stoduto, 1997; Solkhah & Wilens, 1998). Thus, substantial proportions of youth are interested in altering their drinking patterns and likely reflect the heterogeneity in the onset and course of alcohol abuse.

Given the diverse etiological pathways into adolescent alcohol dependence as well as overlapping environmental and behavioral-genetic risks for disorders prevalent during adolescence, treatment samples of adolescent alcohol abusers tend to be heterogeneous with regard to concomitant substances of abuse and psychiatric comorbidity (Chou & Pickering, 1992). Concomitant use of other substances also varies by age and racial/ethnic background. Unfortunately, treatment outcome studies of adolescent alcohol abuse/dependence inconsistently report pretreatment use or posttreatment outcomes independently for individual substances, and no consistent summary measures have been used across studies. Similarly, studies of drug abusing adolescents often fail to separately report alcohol outcomes, although it has been shown that substantial portions of youth relapse using substances other than those for which they entered treatment (Brooks-Gunn et al., 1994; Stice et al., 1998). Given the high substance use comorbidity in adolescent alcohol abuse samples (e.g., 85–90% of treatment samples of alcohol abusing/dependent adolescents smoke cigarettes; Myers & Brown, 1994), variable posttreatment reduction rates across substances (Brown, 1993) and age-related changes in substance prevalence rates, outcome process research findings may be misleading without separate consideration of alcohol and other individual drugs.

Among adult alcohol abusing populations, a variety of concomitant mental health disorders have been associated with poorer treatment outcomes. Reduced resources, social supports and coping skills, as well as elevations in life stress, have been identified as factors in the elevated relapse rates of adults. Several of these factors (e.g., coping skills, social resource networks) are predictive of treatment outcome for adolescents (Brown et al., 1989); however, examination of the role of these factors in the relapse process has not been reported for adolescent alcohol abusers with psychiatric comorbidity.

At present, few models of adolescent alcohol and mental health disorder comorbidity exist (Bukstein et al., 1989). Assessment methodology varies across adolescent studies. Consequently, alcohol- or drug-induced mental health disorders, which may be transient, are seldom distinguished from preexisting and presumably more protracted psychiatric disorders (Chou & Pickering, 1992). Several studies indicate that for at least one common diagnosis, Conduct Disorder (CD), approximately 50% of the cases of CD predate alcohol involvement (Brown, Gleghorn, Schuckit, Myers, & Mott, 1996), and such a primary diagnosis is more resistant to intervention (Whitmore et al., 1997) and adversely impacts long-term outcomes (Myers, Brown, & Mott, 1995) by increasing the risk of adverse consequences when drinking (Stice et al., 1998). In addition, preliminary evidence comparing alcohol and drug use outcomes of adolescents with an alcohol use disorder to adolescents with both an alcohol use disorder and a DMS Axis I mental health disorder showed that significantly poorer outcomes were associated with psychiatric comorbidity (Brown, 1999). Survival analyses further indicate that a greater proportion of youth with alcohol and mental problems relapse and also return to alcohol use earlier in the posttreatment period than adolescents without a concomitant mental health diagnosis (Brown, 1999). Both outcome and process studies for specific psychiatric comorbidity and adolescent alcohol abuse/dependence are needed.

Gender can also be an important factor in treatment outcome. Gender differences exist in alcohol and drug use patterns, presenting mental health-related symptoms, and the pre- and posttreatment needs of adolescent clients with alcohol problems. For example, Rounds-Bryant et al. (Rounds-Bryant, Kristiansen, & Hubbard, 1999) reported that among 3382 adolescents with comparable alcohol, conduct disorder, and ADHD diagnoses, males ($M = 16$ years) engaged in more illegal activities and had a higher prevalence of physical abuse, whereas females ($M = 15$ years) had elevated histories of sexual abuse. Across studies, females evidenced two to four times the rates of maltreatment compared to males with more severe behavioral, emotional, and psychiatric problems. Consequently, it has been inferred that factors affecting the process of outcome following treatment for adolescent alcohol treatment vary across gender. Unfortunately, no consistent pattern of treatment outcome differences has emerged for alcohol abusing adolescent males compared to adolescent females. Gender-specific process-focused treatment outcome research has yet to be conducted.

Ethnic and cultural factors also significantly influence alcohol and drug use and related consequences (Stewart, Brown, & Myers, 1998). Furthermore, ethnic and cultural factors relate to availability of treatment, barriers to treatment, perceived helpfulness of treatment, and retention in treatment. Recent work has shown that the relationship of delinquent behavior to alcohol involvement varies such that certain ethnic groups may benefit more from posttreatment abstinence. For example, Stewart and colleagues found that adverse consequences that are highly associated with alcohol involvement and conduct disordered behavior diminished to a greater extent with abstinence for Hispanics

compared to Caucasians (Stewart et al., 1998). Brooks et al. (Brooks, Stuewig, & LeCroy, 1998) have also shown in a series of studies that ethnic/cultural identity mitigates a number of environmental risks commonly associated with alcohol abuse among youth.

6. Relapse and Posttreatment Functioning

Initial posttreatment experience with alcohol or other drugs has a variable impact on the lives of adolescents. There appears to be considerable variability in the consequences of alcohol use, as well as the likelihood of progressing to regular involvement with substances following the initial posttreatment use of alcohol or drugs. In a series of studies by Brown and her associates (Brown, 1993; Brown, D'Amico, McCarthy, & Tapert, 2001; Brown, Myers, Mott, & Vik, 1994), two clinical cohorts of youth who met criteria for alcohol abuse or dependence were assessed. Approximately one-third of adolescents used alcohol or another drug in the first month after treatment, and up to three-quarters of youth had at least one alcohol or drug experience by 1 year after discharge from inpatient treatment. Six months after treatment, 22% of the treated adolescents had either a single use episode or multiple use episodes, without bingeing and with no identifiable problems associated with their substance use. In this "minor relapse" group, alcohol and marijuana were the most commonly used substances. At 1 year posttreatment, 20% of the sample exhibited this minor relapse pattern and approximately one-third of those who had returned to more severe alcohol or drug use in the first 6 months were either abstaining or were in the minor relapse category. Thus, for adolescents, initial experiences with alcohol or drugs after treatment do not automatically result in a return to pretreatment use rates. Overall, adolescents who reported less alcohol and drug involvement displayed better functioning in several psychosocial domains (Brown et al., 1994). Specifically, abstainers and nonproblem users showed better functioning related to school (e.g., attendance, academic problems) and fewer interpersonal problems. Abstainers also showed improved family functioning (e.g., cohesion, expressiveness) over time. A more recent follow-up study examined substance use across a longer period of time and included the transition from adolescence into young adulthood. Diverse patterns of substance use were found that have not have been evident with shorter follow-up periods (Brown et al., 2001). Specifically, during a 4-year period, only a small percentage of youth (7%) abstained entirely from substances. In addition, transitions into and out of problematic substance use were identified with the longer follow-up, whereby one-fourth of the sample improved initially but did not maintain these changes, and 10% of youth who did not initially improve made positive changes during the extended period (Brown et al., 2001).

Several mediational processes are being examined to determine proximal factors that may influence risks, protective factors, or decisions to drink following

treatment for adolescent alcohol problems. In cognitive and behavioral models of relapse (Marlatt & Gordon, 1980), inadequacies in coping responses for alcohol and drug situations are seen as critical factors in the relapse process. In both cross-sectional and prospective studies (Myers, Brown, & Mott, 1993), coping responses to high risk for relapse situations have been found to be associated with posttreatment drinking. In particular, greater appraisal of risk for relapse (difficulty coping with the situation), lower self-critical cognitive responses, and use of abstinence focused social resources and behavioral responses are predictive of the length of initial abstinence, as well as the number of days drinking posttreatment. Neurocognitive functioning has also been linked to adolescents' posttreatment alcohol and drug relapse and substance use patterns during extended periods of time (Tapert & Brown, 1999). Tapert and Brown (1999) reported that adolescents who continued with heavy substance involvement 4 years after treatment exhibited modest neurocognitive deficits by late adolescence or young adulthood. In addition, severity of withdrawal symptoms experienced by youth was associated with neuropsychological functioning, whereby adolescents who reported *any* withdrawal in the 3 months preceding testing had poorer visuospatial, attentional, and intrusion resistant performance. Given the potential academic and career implications of such findings, further long-term research is needed to examine the stability of these psychosocial and neurocognitive functioning patterns.

In addition to improvements in alcohol and other drug use outcomes, treatment for alcohol use disorders that occur during adolescence is presumed to lead to improvements in other aspects of the functioning of youth. Not only is there considerable variability in the course of alcohol and drug use for adolescents after treatment, but functioning across major life domains fluctuates for these youth as well. Change rates across such areas as school, family, and emotional health indicate that specific types of improvement occur at different times, depending on the degree of control the adolescent has over the particular domain. For example, abstinence from alcohol and other drugs is associated with greater attendance at school early in the posttreatment period. Improvement in grades, however, is not significantly different for youth who do better (e.g., abstain or have a single use episode), compared to those adolescents who return to regular alcohol and drug use until the second grading period following a return to school (Brown et al., 1994). Furthermore, even with sustained abstinence, improvement in family relations occurs even more gradually. In one prospective study (Stewart & Brown, 1994), adolescents demonstrating sustained improvement in alcohol and other drug outcomes after treatment did not differ significantly on family relation measures from their treatment peers who did not return to alcohol or drug abuse until 2 years after treatment. Such a long time course for improvement in family relations has also been demonstrated in families with an abusing parent (Moos, Finney, & Chan, 1981). This suggests that the interpersonal domain, which requires behavioral change for individuals other than the adolescent, may have a slower improvement trajectory, compared to domains reliant only on adolescent behavior (e.g., attending school).

A number of environmental factors have been associated with use outcomes in cross-sectional and prospective studies of adolescents who receive treatment for alcohol problems. Exposure to substances in the environment, particularly through peer networks, is associated with both length of initial abstinence and continuous measures of posttreatment use (Vik et al., 1992). Whereas life stress has been linked to outcomes for adults with alcohol dependence, standard measures of youth stress may initially increase for youth who remain alcohol- and drug-free, compared to peers who return to abuse. In one study that monitored the clinical course following treatment for adolescent alcohol abuse or dependence, self-reported measures of stress increased for adolescents who remained abstinent as measured at 6 months following treatment but were lower than abusing outcome groups by 1 year after treatment (Brown, 1993).

Emotional health outcomes following adolescent alcohol treatment have been examined in several studies, although many questions remain regarding rates and patterns of change in these dimensions, as well as the process whereby such improvements take place. In a sample of 142 adolescents evaluated at 6, 12, and 24 months after treatment, Brown and associates (Brown et al., 1994) reported that posttreatment abstinence was associated with the quality of both interpersonal and emotional functioning. Youth who abstained after treatment, as well as youth who gradually decreased their alcohol and drug involvement during the 2 years after treatment, reported significantly fewer interpersonal problems by late adolescence than those youth who used alcohol and drugs more consistently during this period. Abstinence was less directly linked to the emotional well-being of the adolescent following treatment. Youth with use patterns that deteriorated during the initial 2 years following treatment (greater alcohol and drug involvement despite early success) reported more mental health symptoms (e.g., depression, anxiety) during the follow-up assessments. This finding suggests that, despite improvement in alcohol or drug involvement at 6 months following treatment, youth who exhibit elevations in emotional symptoms are at risk of both increasing emotional problems and accelerating use as they transition to late adolescence.

Few studies of the physical health outcomes of treated youth with an alcohol use disorder have been conducted. In one 5-year prospective comparison, adolescents who received inpatient treatment for an alcohol use disorder were compared to youth from the same communities (Aarons et al., 1999). Community youth were selected to be matched for family history of alcoholism and sociodemographic characteristics. Findings indicated that adolescents with a history of alcohol treatment and those who continued abuse of alcohol and other drugs had more self-reported health problems. In another study, Clark and colleagues (Clark, Lynch, Donovan, & Block, 2001) found that, compared to a community reference group, adolescents with alcohol use disorders had a higher incidence of physical examination abnormalities, more self-reported health problems, and modest but demonstrable liver injury. Brown and colleagues suggest that alcohol use not only has direct negative

effects, such as physical consequences, but may also indirectly impact youth, for example, by increasing the risk of mental health disorders (Brown, 1999; Deas et al., 2000).

Alcohol and drug involvement have been shown to have a deleterious effect on health status among adults, and emerging evidence demonstrates that health problems are likely to become even more evident as early-onset and chronic alcohol and drug abuse during adolescence continues into young adulthood. In addition, although a family history of alcoholism has not been consistently associated with short-term outcomes, a substantial body of research suggests that this behavioral-genetic risk marker substantially elevates long-term risk (Dawson, Harford, & Grant, 1992).

7. Summary and Conclusions

Adolescent alcohol use continues to be a tremendous problem for this nation. Although the field of adolescent treatment for alcohol and alcohol-related problems is growing, there is still a great deal of work to be done. The biological, cognitive, emotional, and social changes that occur during adolescence are profound, and these factors are critical to treatment and influence the process of outcomes following treatment. Increased awareness of the importance of these developmental issues in alcohol use involvement has led to many improvements in both assessing and treating alcohol abuse and dependence in this population.

Many questions remain, however as treatment outcome research for this population is limited compared to adult outcome literature. Reasons for initiating and maintaining use can differ dramatically across developmental stages and need to be examined more thoroughly for adolescents. Although relapse rates are similar among adults and adolescents, for example, the risk factors associated with relapse are quite different, and social factors play a crucial role in adolescent relapse. Understanding the heterogeneity of the adolescent population, for example, differences due to gender, ethnicity, comorbidity, and concomitant use of other substances, is critical from the perspective of both treatment and posttreatment functioning. Further research on the long-term course of treatment is needed so that the effects of developmental factors such as the transition into young adulthood and the stress involved in remaining abstinent can be better understood.

References

- Aarons, G.A., Brown, S.A., Coe, M.T., Myers, M.G., Garland, A.F., Ezzet-Lofstram, R., Hazen, A.L., & Hough, R.L. (1999). Adolescent alcohol and drug abuse and health. *Journal of Adolescent Health* 24, 412–421.
- American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington DC: American Psychiatric Association.

- Azrin, N.H., Acierno, R., Kogan, E.S., & Donohue, B. (1996). Follow-up results of supportive versus behavioral therapy for illicit drug use. *Behaviour Research & Therapy* 34, 41–46.
- Borduin, C.M., Henggeler, S.W., Blaske, D.M., & Stein, R. (1990). Multisystemic treatment of serious juvenile offenders: Long-term prevention of criminality and violence. *International Journal of Offender Therapy and Comparative Criminology* 35, 105–114.
- Breslin, C., Sdao-Jarvie, K., & Pearlman, S. (1998). *Brief Treatment for Youth*, 3rd ed. Toronto: Centre for Addiction and Mental Health, Addiction Research Foundation.
- Brooks, A.J., Stuewig, J., & LeCroy, C.W. (1998). A family based model of Hispanic adolescent substance use. *Journal of Drug Education* 28, 65–86.
- Brooks-Gunn, J., Graber, J.A., & Paikoff, R.L. (1994). Studying links between hormones and negative affect: Models and measures. *Journal of Research on Adolescence* 4, 469–486.
- Brown, S.A. (1993). Recovery patterns in adolescent substance abuse. In J.S. Baer, G.A. Marlatt, & R.J. McMahon (eds.), *Addictive Behaviors Across the Life Span*. Beverly Hills, CA: Sage, pp. 161–183.
- Brown, S.A. (1999). Treatment of adolescent alcohol problems: Research review and appraisal. National Institute on Alcohol Abuse and Alcoholism extramural scientific advisory board (ed.), *Treatment*. Bethesda, MD, pp. 1–26.
- Brown, S.A. (2001). Facilitating change for adolescent alcohol problems: A multiple options approach. In E.F. Wagner & H.B. Waldron (eds.), *Innovations in Adolescent Substance Use Intervention*, pp. 169–189. Oxford: Elsevier Science.
- Brown, S.A., D'Amico, E.J., McCarthy, D.M., & Tapert, S.F. (2001). Four year outcomes from adolescent alcohol and drug treatment. *Journal of Studies on Alcohol* 62, 381–388.
- Brown, S.A., Gleghorn, A., Schuckit, M.A., Myers, M.G., & Mott, M.A. (1996). Conduct disorder among adolescent alcohol and drug abusers. *Journal of Studies on Alcohol* 57, 314–324.
- Brown, S.A., Mott, M.A., & Myers, M.G. (1990). Adolescent alcohol and drug treatment outcome. In R.R. Watson (ed.), *Drug and Alcohol Abuse Prevention*. New Jersey: Humana Press, pp. 373–403.
- Brown, S.A., Myers, M.G., Lippke, L.F., Stewart, D.G., Tapert, S.F., & Vik, P.W. (1998). Psychometric validation of the customary drinking and drug use record (CDDR): A measure of adolescent alcohol and drug involvement. *Journal of Studies on Alcohol* 59, 427–439.
- Brown, S.A., Myers, M.G., Mott, M.A., & Vik, P.W. (1994). Correlates of success following treatment for adolescent substance abuse. *Applied & Preventative Psychology* 3, 61–73.
- Brown, S.A., Tate, S.R., Vik, P.W., Haas, A.L., & Aarons, G.A. (1999). Modeling of alcohol use mediates the effect of family history of alcoholism on adolescent alcohol expectancies. *Experimental & Clinical Psychopharmacology* 7.
- Brown, S.A., Vik, P.W., & Creamer, V.A. (1989). Characteristics of relapse following adolescent substance abuse treatment. *Addictive Behaviors* 14, 291–300.
- Brunk, M., Henggeler, S.W., & Whelan, J.P. (1987). A comparison of multisystemic therapy and parent training in the brief treatment of child abuse and neglect. *Journal of Consulting and Clinical Psychology* 55, 311–318.
- Bukstein, O., & Kaminer, Y. (1994). The nosology of adolescent substance abuse. *American Journal on Addictions* 3, 1–13.
- Bukstein, O.G., Brent, D.A., & Kaminer, Y. (1989). Comorbidity of substance abuse and other psychiatric disorders in adolescents. *American Journal of Psychiatry* 146, 1131–1141.
- Center for Disease Control and Prevention. (1998). *CDC Surveillance Summaries*, vol. 47, No. SS-3.
- Chen, K., & Kandel, D.B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health* 85, 41–47.
- Cherpitel, C.J., Tam, T., Lorraine, M., Caetano, R., & Greenfield, T. (1995). Alcohol and nonfatal injury in the U.S. general population. *Accident Analysis Prevention* 27, 651–661.
- Chou, S.P., Grant, B.F., & Dawson, D.A. (1998). Alcoholic beverage preference and risks of alcohol-related medical consequences: A preliminary report from the national longitudinal alcohol epidemiologic survey. *Alcoholism: Clinical and Experimental Research* 22, 1450–1455.
- Chou, S.P., & Pickering, R.P. (1992). Early onset of drinking as a risk factor for lifetime alcohol-related problems. *British Journal of Addiction* 87, 1199–1204.

- Clark, D., Lynch, K.G., Donovan, J.E., & Block, G.D. (2001). Health problems in adolescents with alcohol use disorders: Self-report, liver injury, and physical examination findings and correlates. *Alcoholism: Clinical and Experimental Research* 25, 1350-1359.
- Compton, W.M., Cottler, L.B., Dorsey, K.B., Spitznagel, E.L., & Mager, D.E. (1996). Comparing assessments of DSM-IV substance dependence disorders using CIDI-SAM and SCAN. *Drug and Alcohol Dependence* 41, 179-187.
- Cornelius, J.R., Bukstein, O.G., Birmaher, B., Salloum, I.M., Lynch, K., Pollock, N.K., Gershon, S., & Clark, D. (2001). Fluoxetine in adolescents with major depression and an alcohol use disorder: An open-label trial. *Addictive Behaviors* 26, 735-739.
- Cornelius, J.R., Maisto, S.A., Pollock, N.K., Martin, C.S., Salloum, I.M., Lynch, K.G., & Clark, D.B. (in press). Rapid relapse generally follows treatment for substance use disorders among adolescents. *Addictive Behaviors*.
- Cottler, L.B., Robins, L.N., & Helzer, J.E. (1989). The reliability of the CIDI-SAM: A comprehensive substance abuse interview. *British Journal of Addiction* 84, 801-814.
- Cottler, L.B., Schuckit, M.A., Helzer, J.E., Crowley, T.J., Woody, G., Nathan, P., & Hughes, J. (1995). The DSM-IV field trial for substance use disorders: Major results. *Drug and Alcohol Dependence* 38, 59-69.
- D'Amico, E.J., & Fromme, K. (2002). Brief prevention for adolescents. *Addiction* 97, 563-574.
- D'Amico, E.J., Metrik, J., McCarthy, D.M., Frissell, K.C., Appelbaum, M., & Brown, S.A. (2001). Progression into and out of binge drinking among high school students. *Psychology of Addictive Behaviors* 15, 341-349.
- Dawson, D.A., Harford, T.C., & Grant, B.E. (1992). Family history as a predictor of alcohol dependence. *Alcoholism: Clinical & Experimental Research* 16, 572-575.
- Deas, D., Riggs, P., Langenbucher, J., Goldman, M., & Brown, S. (2000). Adolescents are not adults: Developmental considerations in alcohol users. *Alcoholism: Clinical and Experimental Research* 24, 232-237.
- DeWit, D.J., Offord, D.R., & Wong, M. (1997). Patterns of onset and cessation of drug use over the early part of the life course. *Health Education & Behavior* 24, 746-758.
- Donovan, J., & Jessor, R. (1985). Structure of problem behavior in adolescence and young adulthood. *Journal of Consulting and Clinical Psychology* 53, 890-904.
- Ellickson, P.L., Hays, R.D., & Bell, R.M. (1992). Stepping through the drug use sequence: Longitudinal scalogram analysis of initiation and regular use. *Journal of Abnormal Psychology* 101, 441-451.
- Friedman, A.S., Terras, A., & Ali, A. (1998). Differences in characteristics of adolescent drug abuse clients that predict to improvement: For inpatient treatment versus outpatient treatment. *Journal of Child & Adolescent Substance Abuse* 7, 97-119.
- Harris, J.C. (1995). *Developmental Neuropsychiatry*, Vol. 1: *The fundamentals*, Vol. 2: *Assessment, Diagnosis, and Treatment of Developmental Disorders*. New York: Oxford University Press.
- Harrison, P.A., Fulkerson, J.A., & Beebe, T.J. (1998). DSM-IV substance use disorder criteria for adolescents: A critical examination based on a statewide school survey. *American Journal of Psychiatry* 155, 486-492.
- Henggeler, S.W. (1998). *Multisystemic Therapy*. Denver, CO: C & M Press.
- Henggeler, S.W., Melton, G.B., & Smith, L.A. (1992). Family preservation using multisystemic therapy: An effective alternative to incarcerating serious juvenile offenders. *Journal of Consulting and Clinical Psychology* 60, 953-961.
- Henggeler, S.W., Rodick, J.D., Borduin, C.M., Hanson, C.L., Watson, S.M., & Urey, J.R. (1986). Multisystemic treatment of juvenile offenders: Effects on adolescent behavior and family interactions. *Developmental Psychology* 22, 132-141.
- Hser, Y.-I., Grella, C.E., Hubbard, R.L., Hsieh, S.-C., Fletcher, B.W., Brown, B.S., & Anglin, M.D. (2001). An evaluation of drug treatments for adolescents in 4 US cities. *Archives of General Psychiatry* 58, 689-695.
- Hubbard, R.L., Cavanaugh, E.R., Graddock, S.G., & Rachel, J.V. (1983). Characteristics, behaviors and outcomes for youth in TOPS study (Contract No. 271-79-3611). Research Triangle Park, NC: Research Triangle Institute. National Institute on Drug Abuse.

- Huttenlocher, P.R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia* 28, 517-527.
- Joanning, H., Quinn, W., Thomas, F., & Mullen, R. (1992). Treating adolescent drug abuse: A comparison of family systems therapy, group therapy, and family drug education. *Journal of Marital and Family Therapy* 18, 345-356.
- Johnston, L.D., O'Malley, P.M., & Bachman, J.G. (2000). National survey results on drug use from the Monitoring the Future Study, 1975-1999, Vol. 1. *Secondary school students*. Rockville, MD.
- Kaminer, Y. (1995). Issues in the pharmacological treatment of adolescent substance abuse. *Journal of Child & Adolescent Psychopharmacology* 5, 93-106.
- Kaminer, Y., Burleson, J.A., Blitz, C., Sussman, J., & Rounsville, B.J. (1998). Psychotherapies for adolescent substance abusers: A pilot study. *The Journal of Nervous and Mental Disease* 186, 684-690.
- Kandel, D., & Faust, R. (1975). Sequence and stages in patterns of adolescent drug use. *Archives of General Psychiatry* 32, 923-932.
- Kandel, D.B., Yamaguchi, K., & Chen, K. (1992). Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies on Alcohol* 53, 447-457.
- Kelly, J.F., Myers, M.G., & Brown, S.A. (2000). A multivariate process model of adolescent 12-step attendance and substance use. *Psychology of Addictive Behaviors* 24, 376-389.
- Kolb, B., & Fantie, B. (1997). Development of the child's brain and behavior. In C.R. Reynolds & E. Fletcher-Janzen (eds.), *Handbook of Clinical Child Neuropsychology*, 2nd ed. New York: Plenum, pp. 17-41.
- Lewinsohn, P.M., Rohde, P., & Seeley, J.R. (1996). Alcohol consumption in high school adolescents: Frequency of use and dimensional structure of associated problems. *Addiction* 91, 375-390.
- Lewis, R.A., Piercy, F.P., Sprenkle, D.H., & Trepper, T.S. (1990). Family-based interventions for helping drug-abusing adolescents. *Journal of Adolescent Research* 50, 82-95.
- Liddle, H.A., & Dakof, G.A. (1995). Family-based treatment for adolescent drug use: State of the science. In E.R.D. Czechowicz (ed.), *Adolescent Drug Abuse: Clinical Assessment and Therapeutic Interventions*. Rockville, MD: National Institute on Drug Abuse.
- Marlatt, G.A., Baer, J.S., Kivlahan, D.R., Dimeff, L.A., Larimer, M.E., Quigley, L.A., Somers, J.M., & Williams, E. (1998). Screening and brief intervention for high-risk college student drinkers: Results from a 2-year follow-up assessment. *Journal of Consulting and Clinical Psychology* 66, 604-615.
- Marlatt, G.A., & Gordon, J.R. (1980). Determinants of relapse: Implications for the maintenance of behavior change. In P.O. Davidson & S. M. Davidson (eds.), *Behavioral Medicine: Changing Health Lifestyles*. Elmsford, NY: Pergamon, pp. 410-452.
- Martin, C.S., Clifford, P.R., Maisto, S.A., Earleywine, M., Kirisci, L., & Longabaugh, R. (1996a). Polydrug use in an inpatient treatment sample of problem drinkers. *Alcoholism: Clinical and Experimental Research* 20, 413-417.
- Martin, C.S., Kaczynski, N.A., Maisto, S.A., Bukstein, O.M., & Moss, H.B. (1995). Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol* 56, 672-680.
- Martin, C.S., Kaczynski, N.A., Maisto, S.A., & Tarter, R.E. (1996b). Polydrug use in adolescent drinkers with and without DSM-FV alcohol abuse and dependence. *Alcoholism: Clinical and Experimental Research* 20, 1099-1108.
- Martin, C.S., Langenbucher, J.W., Kaczynski, N.A., & Chung, T. (1996c). Staging in the onset of DSM-IV alcohol symptoms in adolescents: Survival/hazard analyses. *Journal of Studies on Alcohol* 57, 549-558.
- Martin, C.S., Pollock, N.K., Bukstein, O.G., & Lynch, K.G. (2000). Inter-rater reliability of the SCID alcohol and substance use disorders section among adolescents. *Drug and Alcohol Dependence* 59, 173-176.
- Martin, C.S., & Winters, K.C. (1998). Diagnosis and assessment of alcohol use disorders among adolescents. *Alcohol Health & Research World* 22, 95-105.

- Meyers, K., Hagan, T.A., Zanis, D., Webb, A., Frantz, J., Ring-Kurtz, S., Rutherford, M., & McLellan, A.T. (1999). Critical issues in adolescent substance use assessment. *Drug and Alcohol Dependence* 55, 235–246.
- Mikulich, S.K., Hall, S.K., Whitmore, E.A., & Crowley, T.J. (2001). Concordance between DSM-III-R and DSM-IV diagnoses of substance use disorders in adolescents. *Drug and Alcohol Dependence* 61, 237–248.
- Miller, W.R., Brown, J.M., Simpson, T.L., Handmaker, N.S., Bien, T.H., Luckie, L.F., Montgomery, H.A., Hester, R.K., & Tonigan, J.S. (1995). What works? A methodological analysis of the alcohol treatment outcome literature. In R.K. Hester & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches*. Boston, MA: Allyn & Bacon, pp. 12–44.
- Monti, P.M., Colby, S.M., Barnett, N.P., Spirito, A., Rohsenow, D.J., Myers, M., Woolard, R., & Lewander, W. (1999). Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *Journal of Consulting and Clinical Psychology* 67, 989–994.
- Moos, R.H., Finney, J.W., & Chan, D.A. (1981). The process of recovery from alcoholism: I. Comparing alcoholic patients and matched community controls. *Journal of Studies on Alcohol* 42, 383–402.
- Morgenstern, J., Labouvie, E., McCrady, B.S., Kahler, C.W., & Frey, R.M. (1997). Affiliation with Alcoholics Anonymous after treatment: A study of its therapeutic effects and mechanisms of action. *Journal of Consulting and Clinical Psychology* 65, 768–777.
- Myers, M.G., & Brown, S.A. (1990). Coping and appraisal in potential relapse situations among adolescent substance abusers following treatment. *Journal of Adolescent Chemical Dependency* 1, 95–115.
- Myers, M.G., & Brown, S.A. (1994). Smoking and health in substance abusing adolescents: A two year follow-up. *Pediatrics* 93, 561–566.
- Myers, M.G., Brown, S.A., & Mott, M.A. (1993). Coping as a predictor of adolescent substance abuse treatment outcome. *Journal of Substance Abuse* 5, 15–29.
- Myers, M.G., Brown, S.A., & Mott, M.A. (1995). Pre adolescent conduct disorder behaviors predict relapse and progression of addiction for adolescent alcohol and drug abusers. *Alcoholism: Clinical and Experimental Research* 19, 1527–1536.
- Myers, M.G., Brown, S.A., & Vik, P.W. (1998). Adolescent substance use problems. In E.J. Mash & R.A. Barkly (eds.), *Treatment of Childhood Disorders*, 2nd ed. New York: Guilford.
- Nelson, C.B., & Wittchen, H.-U. (1998). DSM-IV alcohol disorders in a general population sample of adolescents and young adults. *Addiction* 93, 1065–1077.
- O'Malley, P.M., Johnston, L.D., & Bachman, J.G. (1998). Alcohol use among adolescents. *Alcohol, Health, & Research World* 22, 85–93.
- Pollock, N.K., & Martin, C.S. (1999). Diagnostic orphans: Adolescents with alcohol symptoms who do not qualify for DSM-IV abuse or dependence diagnoses. *American Journal of Psychiatry* 156, 897–901.
- Randall, J., Henggeler, S.W., Cunningham, P.B., Rowland, M.D., & Swenson, C.C. (2001). Adapting multisystemic therapy to treat adolescent substance abuse more effectively. *Cognitive and Behavioral Practice* 8, 359–366.
- Reich, W., Shayla, J.J., & Taibelson, C. (1992). *The Diagnostic Interview for Children and Adolescents-Revised (DICA-R)*. St. Louis, MO: Washington University.
- Roberts, R.E., Solovitz, B.L., Chen, Y.W., & Casat, C. (1996). Retest stability of DSM-III-R diagnoses among adolescents using the Diagnostic Interview for Children (DISC-2.1 C). *Journal of Abnormal Child Psychology* 24, 349–362.
- Rohde, P., Lewinsohn, P.M., Kahler, C.W., Seeley, J.R., & Brown, R.A. (2001). Natural course of alcohol use disorders from adolescence to young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry* 40, 83–90.
- Rounds-Bryant, J.L., Kristiansen, P.L., & Hubbard, R.L. (1999). Drug abuse treatment outcome study of adolescents: A comparison of client characteristics and pretreatment behaviors in three treatment modalities. *American Journal of Drug & Alcohol Abuse* 25, 573–591.
- Rush, T.V. (1979). Predicting treatment outcomes for juvenile and young adult clients in the Pennsylvania substance-abuse system. In G.M. Beschner & A.S. Friedman (eds.), *Youth Drug Abuse: Problems, Issues and Treatment*. Lexington, MA: Lexington Books.

- Sells, S.B., & Simpson, D.D. (1979). Evaluation of treatment outcome for youths in the Drug Abuse Reporting Program (DARP): A followup study. In G.M. Beschner & A.S. Friedman (eds.), *Youth Drug Abuse: Problems, Issues and Treatment*. Lexington, MA: Lexington Books.
- Shaffer, D., Fischer, P., & Dulcan, M. (1996). The NIMH diagnostic interview schedule for children (DISC 2.3): Description, acceptability, prevalences, and performance in the MECA study. *Journal of the American Academy of Child and Adolescent Psychiatry* 35, 865–877.
- Smart, R.G., & Stoduto, G. (1997). Treatment experiences and need for treatment among students with serious alcohol and drug problems. *Journal of Child & Adolescent Substance Abuse* 7, 63–72.
- Solkhah, R., & Wilens, T.E. (1998). Pharmacotherapy of adolescent AOD use disorders. *Alcohol, Health, & Research World* 22, 122–126.
- Stewart, D.G., & Brown, S.A. (1995). Withdrawal and dependency symptoms among adolescent alcohol and drug abusers. *Addiction* 90, 627–635.
- Stewart, D.G., Brown, S.A., & Myers, M.G. (1998). Antisocial behavior and psychoactive substance involvement among Hispanic and non-Hispanic Caucasian adolescents in substance abuse treatment. *Journal of Child & Adolescent Substance Abuse* 6, 1–22.
- Stewart, M.A., & Brown, S.A. (1994). Family functioning following adolescent substance abuse treatment. *Journal of Substance Abuse* 5(4), 327–339.
- Stice, E., Myers, M.G., & Brown, S.A. (1998). A longitudinal grouping analysis of adolescent substance use escalation and de-escalation. *Psychology of Addictive Behaviors* 12, 14–27.
- Szapocznik, J., Kurtines, W.M., Foote, F., Perez-Vidal, A., & Hervis, O. (1986). Conjoint versus one-person family therapy: Further evidence for the effectiveness of conducting family therapy through one person with drug-abusing adolescents. *Journal of Consulting and Clinical Psychology* 54, 395–397.
- Szapocznik, J., Kurtines, W.M., & Hervis, O. (1983). Conjoint versus one-person family therapy: Some evidence for the effectiveness of conducting family therapy through one person. *Journal of Consulting and Clinical Psychology* 51, 889–899.
- Tapert, S.F., & Brown, S.A. (1999). Neuropsychological correlates of adolescent substance abuse: Four year outcomes. *Journal of the International Neuropsychological Society* 5, 475–487.
- Tschann, J.M., Adler, N.E., Irwin, C.E., Jr., Millstein, S.G., Turner, R.A., & Kegeles, S.M. (1994). Initiation of substance use in early adolescence: The roles of pubertal timing and emotional distress. *Health Psychology* 13, 326–333.
- Vik, P.W., Grizzle, K., & Brown, S.A. (1992). Social resource characteristics and adolescent substance abuse relapse. *Journal of Adolescent Chemical Dependency* 2, 59–74.
- Wagner, E.S., Brown, S.A., Monti, P., Myers, M.G., & Waldron, H.B. (1999). Innovations in adolescent substance abuse and prevention. *Alcoholism: Clinical and Experimental Research* 23, 236–249.
- Waldron, H.B., Brody, J.L., & Slesnick, N. (2001a). Integrative behavioral and family therapy for adolescent substance abuse. In P.M. Monti, S.M. Colby, & T.A. O'Leary (eds.), *Adolescents, Alcohol, and Substance Abuse: Reaching Teens Through Brief Interventions*. New York: Guilford, pp. 216–243.
- Waldron, H.B., Slesnick, N., Brody, J.L., & Peterson, T.R. (2001b). Treatment outcomes for adolescent substance abuse 4- and 7-month assessments. *Journal of Consulting and Clinical Psychology* 69, 802–813.
- Whitmore, E.A., Mikulich, S.K., Thompson, L.L., Riggs, P.D., Aarons, G.A., & Crowley, T.J. (1997). Influences on adolescent substance dependence: Conduct disorder, depression, attention deficit hyperactivity disorder, and gender. *Drug & Alcohol Dependence* 47, 87–97.
- Wilens, T.E., Biederman, J., Abrantes, A.M., & Spencer, T.J. (1996). A naturalistic assessment of protriptyline for attention-deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 35, 1485–1490.
- Wilens, T.E., Biederman, J., Abrantes, A.M., & Spencer, T.J. (1997). Clinical characteristics of psychiatrically referred adolescent outpatients with substance use disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 36, 941–947.
- Winters, K.C. (1999). Treating adolescents with substance use disorders: An overview of practice issues and treatment outcome. *Substance Abuse* 20, 203–225.
- Winters, K.C., Stinchfield, R.D., Fulkerson, J., & Henly, G.A. (1993). Measuring alcohol and cannabis use disorders in an adolescent clinical sample. *Psychology of Addictive Behaviors* 7, 185–196.

Treatment for Alcohol-Related Problems: Special Populations: Research Opportunities

Edith S. Lisansky Gomberg

Abstract. For the subgroups indicated, a few questions/issues are relevant to all three (women, elderly, minorities):

1. Heterogeneity of the special populations, for example, Hispanic-Americans are from different countries with different cultures. Women and the elderly vary by age, education, income, social class, health status, etc., to say nothing of ethnicity/color/religion.
2. Of therapy modalities, professional and indigenous, which are more efficacious?
3. Are group-specific therapies needed, or will sensitivity to a particular group work as well?

Women

Stereotypes and myths have prevailed, for example, the long-standing belief that women have poorer prognoses than male alcoholics. When female and male alcoholics are compared, women report more positive family history, a later onset of drinking and problems, more marital disruption, more comorbidity, etc. The review of treatment outcomes (Vannicelli, 1986) showed few significant gender differences in outcomes.

Research recommendations include biological and genetic studies, women's view of and use of therapeutic modalities, and outcome studies of different modalities, including all female facilities.

Elderly

Medications are used more by older patients, and such patients are more likely to experience adverse drug reactions. In the moderate social use of alcohol, there are conflicting reports and the extent of elderly use awaits decisive study.

The etiology of problem drinking by older persons is studied rarely. An attempt has been made to explain onset later in life (vs. earlier onset) based on the stresses of aging (loss, loneliness, health problems, etc.); research results have not been supportive. Consequences of older persons' heavy

drinking seems to be most often alcohol-related medical disorders, although there are often familial and social consequences. Atkinson (1995) recommended the development of elder-specific outcome measures, study of the efficacy of different treatment modalities, and study of the efficacy of treatment for patients in elder-specific and mixed age groups, etc.

Minorities

Each of the federally mandated minority groups in the United States is heterogeneous. The epidemiology of use and abuse of alcohol and other drugs is well studied, but treatment issues are not.

American Indians

There are more than 200 tribes; each has its own customs and culture. Some tribes are abstinent; others have big problems with abuse of alcohol, and other drugs. Orthodox treatment methods, used by professional counselors and therapists, have not worked very well. Recommendation: study of traditional Indian forms of healing practices combined with other treatment; this would be a culture-sensitive model.

Black Americans

This includes not only African-Americans but people from the Caribbean, Central and South America, etc. Among African-Americans, there is a history of ambivalence toward alcohol: on the one hand, a tolerant "nightclub culture" and on the other, church beliefs in temperance and abstinence. There is "respectable drinking" and "problem drinking," most often defined as solitary or public drinking. The primary source of support is considered familial, so people tend to be distrustful of therapy from "strangers." They are anonymous in promoting sobriety and study of subcultural norms and the history of slavery. Earlier ethnographic works (Liebow, 1967) were of "street-corner men," slum dwellers, ghetto norms; recommended: studies of middle-class African-American life and drinking behaviors.

Asian-Americans

A study in Los Angeles reports differences among Chinese, Japanese, Filipinos, and Koreans in drinking beliefs and behavior. Of these groups, the Japanese in Japan and the Japanese-Americans report the largest number of heavy drinkers. It is, however, considered a private matter, even when associated with social problems. Interestingly, there is an organization called the All Nippon Sobriety Association (like Alcoholics Anonymous). Recommendations: studies of generational differences among Japanese-Americans in use and efficacy of treatment. For the Chinese-Americans, who are fairly permissive about older persons' drinking and share a belief in the health benefits of alcohol, a gender/gerontological study is recommended.

Hispanic-Americans

As a total group, they drink more and present more alcohol-related problems than other immigrant minorities. Age, ethnicity, and gender patterns in permissiveness to drink need to be explored. Treatment sought is often in pentecostal churches and Centros for Espiritismo. Hispanics are not likely to seek help in formal clinical settings which emphasize alcohol consumption as the basic, core problem. They are more likely to seek out and be responsive to the perception of their drinking problem as sin and a rejection of Jesus.

It is not that minorities do not recognize problems and seek out help. They are not likely to seek out the health profession's offering of outpatient clinics, residential treatments, etc.

In examining the research needs of treatment within so-called special populations, it is a good idea to start with the common question, that characterizes all discussion of alcohol problems treatment within *all* of these groups: the basic question is whether treatments, as acceptable and administered to white males, youth and adult, should be applicable to population subgroups or whether there should be gender-specific, elder-specific, or minority-specific treatments.

The arguments, pro and con, have often been based on contemporary politics and the Zeitgeist. Thus, although there is heightened awareness now of the needs of subgroups (particularly those with a history of second-class citizenship), it should be emphasized that we are not trying to be all-inclusive. We have not, for example, included those who are a special group by sexual orientation or by reason of disability.

1. Women

We begin almost a half-century ago. A review of the literature, such as it was (Lisansky, 1957) made a number of points:

1. The point of view that women problem drinkers were "much more abnormal" than male problem drinkers (Karpman, 1948) were once widely held. The reasoning was that women was more repressed, more tense, and that loss of control is "more vehemently expressed." Women were seen as management problems and had poorer prognosis in treatment. Current findings do show more comorbidity in women than among male problem drinkers, and it is also true that women problem drinkers manifest more depressive symptoms than men; that is true for the general population as well as for alcoholics.
2. There was a description of women patients as more *variable* than male. It was not clear whether the variability was in etiology, in onset situations, and/or in maintenance of the problem drinking.
3. It was also thought that women were more likely to begin heavy/problem drinking, related to *specific stress*, that is, "a definite life situation" (Wall, 1937). It was not clear whether such a report was based on a need to defend oneself. One definite life situation widely reported in the literature is the presence of a significant other (frequently a spouse) who is a heavy drinker.
4. The association between female heavy drinking and *sexual promiscuity* was made, although it was never clear whether the female became more sexually aggressive under the influence or whether she was more vulnerable to sexual assault. The problems with examining that association are that (a) such a view was part of a judgmental condemnation of the woman who drinks too much and an association between prostitution and alcoholism and (b) sexual mores have changed so remarkably in the last halfcentury that it would be difficult to establish such an

association at this time. The definition of *promiscuity* is unclear at this moment, and it was not recognized that a large proportion of women alcoholics drinks at home.

5. There was a hypothesis that women had their first drink at a *later age* than men and that the shift from controlled to uncontrolled drinking was more rapid, that is, *telescoped*. There has been evidence that these observations are valid for young, middle-aged, and older women; whether it is equally valid for adolescent problem drinkers needs investigation.
6. A linkage between female alcoholism and menstruation, parturition, and menopause was postulated. Some linkages do show up in the research across the decades. The role of premenstrual tensions, difficulty in conception and in birth, and possibly menopausal problems do play a role.
7. There has been early evidence that medical effects particularly hepatic effects, occur more readily among women heavy drinkers than male heavy drinkers. This difference in vulnerability occurs even when the genders are matched carefully for alcohol intake related to body weight.

Note that these early points made by investigators did not include discussions of genetics. In a study of 301 alcoholic women in treatment, matched with a nonalcoholic, age-matched and social class-matched group of 137 women, the alcoholic women reported significantly more drinking problems in their early and recent family histories (Gomberg, 1989a). Interestingly, although the alcoholic parent was usually the father, this did not affect the women's closeness to father.

Nor did these early studies look at role behaviors, personality traits, or other diagnostic features. In our study, we found the women in the alcoholic sample left school earlier, left home earlier, and married at an earlier age than nonalcoholics. Marital difficulties and a heavy drinking spouse occurred more frequently among alcoholic women.

One of the main difficulties in discussing problem drinking women is the fact that this embraces a wide age group and there are significant age differences, for example, the younger women are more likely to drink in public, to use other drugs, and to report childhood temper tantrums. It was our interpretation that *impulsivity* was more of an issue with younger alcoholic women, and *disenchantment/depression* more of an issue with older ones. That younger alcoholic women also manifest depression may be seen in their relative suicide risk, the combination of impulsivity and depression (Gomberg, 1989b).

There has always been the question whether women heavy drinkers should be compared with heavy drinking men or whether they should be studied and compared with other women; both approaches are relevant. Men and women when young, seem to be similarly motivated by pleasure-seeking, but young women show different expectancies about the effects of alcohol; unlike young men who show less anxiety when drinking with women, women show more anxiety when drinking with males (Marlatt, 1986). When male and female

alcoholics are compared, these are the major differences that emerge:

1. Women report more positive family histories.
2. Men begin drinking at a younger age, and onset of alcoholism is earlier.
3. Women more frequently report a spouse/lover who is a heavy drinker.
4. Men are more likely to drink in public places.
5. Men are more likely to present an early history of impulsive, acting out behaviors.
6. Women report more marital disruption.
7. Women more frequently report dual diagnoses.

On a practical level, when men and women alcoholics in treatment are compared, the women have fewer financial resources and experience more family pressure to terminate treatment. It also appears to be true that women present with more guilt, usually related to the maternal role. The consequences of heavy drinking vary somewhat in men and women: medical problems such as DTs, blackouts, and accidents are more often presented by men, but women are more vulnerable to hepatic disorder. Occupational and legal consequences that relate to gender differences in social role and drinking behaviors differ. There has been, for years, a debate over stigma: it is usually assumed that there is greater stigma for women, but a Finnish Survey (International Council on Alcohol and Addictions, 1988) concluded that, "... men are more likely to have been criticized than women."

Treatment procedures for women who present at treatment facilities have included similar modalities: medication, counseling, group therapy, etc. There are questions of female use of residential versus outpatient facilities and a much-debated question about whether therapists of the same gender are preferable. Some treatment facilities (very limited) are oriented toward women and their children. A recent series of reports on the efficacy of treatments is confined to drug abusing women (cocaine primarily) (Drugs and Society, 1998) with reports on therapeutic communities, prison populations, a treatment community for women with their children, and a comparison of residential treatment for women (mean age 28) with their children and women without children.

Despite the fact that there are, to this very day, more research reports with male subjects than with mixed or female groups, a therapist needs gender-oriented sensitivity to the female patient's history, needs, and life situation. As stated recently by Martin et al. (1999):

... future intervention studies should assess contextual factors (e.g., gender differences in drinking contexts), test gender-sensitive materials, and seek to identify the most effective venues for implementing interventions... (p. 358)

There have been three NIAAA research conference reports. The first was a report on a 1978 workshop including one discussion (Blume, 1980) about treatment: she reviews the debate about the efficacy of group therapy versus individual treatment but emphasizes the need for all-female group work.

Blume also notes the work on marital therapy, behavior therapy, and chemotherapy, but when she was summarizing the available literature, it was almost entirely confined to male alcoholics. Her recommendations about case finding are of interest: industrial programs, driver rehabilitation, outreach to physicians, study of fetal alcohol effects, TV programs directed toward housewives, etc.

The second NIAAA conference women in alcohol was held in 1984 and published in 1986. Vannicelli (1986) reviewed treatment outcome studies, first surveying the outcome literature and noting that women are quite underrepresented. The old myths that women have poorer prognoses still exist, but she points out that there is research evidence of more "negative social consequences and more barriers" to women entering treatment. Reviewing all outcome studies in the prior 30 years,

"...we find 43 studies in which there were no differences between males and females, 7 that show females doing better, and 5 in which males had better outcomes ..." (p. 141).

Vannicelli also reviewed 95 studies on treatment modalities, and she concluded that there were very few data on the questions of (a) group versus individual therapy, (b) value of family therapy, (c) the need for women to be treated separately, and (d) the value of a female therapist. There was little evidence to support the beliefs of poorer prognosis, women alcoholics' need for separate facilities, and for treatment by female therapists. In fact, the limited available evidence on prognosis did not show gender differences at all.

The third conference had no reports on treatment at all except for a few lines in the commentary about future directions (Martin et al., 1999). This title of conference was Women and Alcohol: Issues for Prevention Research.

Recent work in gender comparison has focused on issues of socialization: Are boys the weaker sex? Why girls do better in the real world (U.S. News and World Report, July 30, 2001, pp. 40-47). The controversy deals with the question of gender socialization: whether the male or female role is more adaptive in contemporary society.

And a series of papers, sponsored by the European Union, Final Project Action, "Alcohol Consumption and Alcohol Problems, June 1999; appeared in *Substance Abuse, Journal of AMERSA*, Association for Medical Education and Research in Substance Abuse, in March 2001. The first paper looked at the comparability of the surveys from three points of view: methodological, sales estimates, and types of questions used. The conclusions were that methodological differences do not permit comparisons in alcohol beverage sales. Also, the simpler the questions, the more likely the underestimation of heavy drinking comparisons of the two sexes. The second paper looked for evidence about convergence because it compares findings in repeated surveys in Finland, Germany, Holland, and Switzerland. Only one country—Finland—supported the convergence hypothesis (men and women's converging over time).

However, such convergence could be due to the convergence of the sexes in professions and lifestyle, to the longer time gap between first and second surveys, or to the modest amount of female drinking apparent in the first survey in Finland. The third paper examined alcohol-related mortality in eight European countries. The authors emphasize methodological limits and recommend procedures for a more reliable calculation of the estimates.

The final paper covered age, education, employment status, marital status, and parenthood in comparing gender differences in drinking patterns in nine European countries. Three different societal patterns make for egalitarian drinking patterns of the sexes: drinking well integrates in everyday life, women have low employment status, and a high level of integration in drinking. Divorced people consistently drank more often and in greater quantities. Finally, parenthood was profoundly and consistently associated with women's drinking patterns. Parenthood seems to protect women from heavy drinking (Rutledge & Syer, QJSA 62(4) 2001, pp. 457-468).

There have been several recent papers dealing with issues of gender differences. When young adults are compared in the role of stress, tension reduction, motives to drink, and personality, only the males in group 4 (21 years of age) show higher tension reduction and highest stress (more negative life events) associated with higher levels of heavy drinking. An obvious limitation of the study is the limited age group sampled, although several explanations are offered to account for the one significant linkage.

A report on psychopathology in drug-dependent women with/without comorbid alcohol dependence (Miles et al., 2001) concluded that women with alcoholism comorbidity require more intense interventions.

A study of Mexican-American women who report violence and their alcohol intake shows a strong association between abuse and intake; this has been noted in different ethnic groups and suggests a tie between abuse and alcohol among women (Lown & Vega, 2001). Needed now is the establishment of temper older of abuse alcohol.

And, finally there is a study of "unexpected gender differences, that is, in hostility, when men and women in treatment are compared (Robinson et al., 2001). Expected differences in comparisons of anxiety and depression (high scores for women) were obtained, and several explanations are offered for the difference in aggression scores.

Over the years, we have learned a fair amount about women's drinking and alcohol abuse: patterns, behaviors, consequences. What we have *not* done is study treatment. Several books about women and alcohol problems include a chapter devoted to treatment modalities and outcomes. An early review (Annis & Liban, 1980) raised a number of questions:

1. poorer prognosis for women?—same evaluation as Vannicelli's (1986), that is, no evidence of poorer response to treatment;
2. prognostic factors? These include demographics, use of other drugs, physical complications, psychiatric diagnoses, personality test scores,

and pretreatment factors, that is, referral by AA, voluntary admission, etc. Again, the literature yields an ambiguous response: some studies show minimal gender difference, and others show different gender prognostic factors.

On the question of "treatment specificity," Annis and Liban emphasize the heterogeneity of the female alcoholic population and mention several suggestions, for example, family intervention techniques and environmental intervention strategies.

Discussion by Lex (1994) brings up a number of relevant issues; for example, Lex points to the lack of studies focused on biological variables. The author also points out the barriers to treating of female alcoholics: stereotyped thinking about poorer prognosis, greater depression and mood liability, limited potential for change, and infantilization. It is believed that women alcoholics are poorly motivated, very ambivalent about treatment, and are more difficult to engage in therapy. It has been noted that women problem drinkers are more likely to seek help for specific problems: marital, family, emotional or medical. As for the question of persistence in treatment, Lex states that women are more likely than men to acknowledge problems with "...family, friends, and finances," but they also apparently have more difficulty in establishing trust. Finally, a differentiation needs to be made between primary and secondary alcoholism (Schuckit et al., 1969; Turnbull, 1988). In primary alcoholism, the alcoholism appears first and either concomitantly or afterwards, depression; in secondary alcoholism, the first diagnosis would be depression; the alcoholism follows.

Walitzer and Connors (1997) discuss gender issues in treatment use and in treatment effectiveness. Although women have been underrepresented in alcoholism treatment facilities, a recent report by SAMHSA (1998), the National Drug and Alcoholism Treatment Unit Survey, indicates some change: more males were in treatment for alcoholism, but higher proportions of women were in treatment for drug abuse, and equal proportions of the genders were being treated for alcohol/drug abuse. Women apparently will use health care services which relate to gender biases and sex role stereotypes; thus, they are overrepresented in treatment for depression but underrepresented in treatment for alcoholism. One model of services use suggests that women are more likely to use services with more professional employees, treatment services for children, and aftercare services. Walitzer and Connors again emphasize the absence of well-designed studies on the efficacy of treatment for female alcoholism and report the lack of clear gender differences in outcome.

1.1. Recommendations

1. Needed are more studies of neurophysiological and hormonal relationships to female alcohol problems—antecedent and consequent.
2. More detailed genetic studies, for example., which parent? Sibling? Other relative? Amount of contact? Relationships, etc? We did not find

younger women alcoholics reporting more positive family histories than older groups (Gomberg, 1991).

3. More research on women who abuse alcohol versus those who abuse both alcohol and drugs.
4. Women problem drinkers' attitudinal responses to different treatment modalities. Do women prefer counseling or behavioral therapy?
5. National, large sample studies of men's/women's use of alcoholism treatment facilities: reasons for entry?
6. Four decades ago, Wallerstein (1957) published a study of hospitalized alcoholic veterans: four subgroups were assigned to one of four treatment modalities:
7. A case study or ethnographic approach to chart the life histories of women including their stresses and difficulties, coping mechanisms, barriers to treatment, etc.

2. The Elderly

The use and abuse of alcohol by older people is a relatively new field of exploration. With the extension of life expectancy, there is simply a larger pool of people to study; that pool grows to become a larger proportion of the population every decade (nor is this true for the United States alone. It is true of all developed countries and many of the less developed countries). There are more, older women than older men; the sex ratio is close to 150 women for every 100 men. The minority elderly population it is projected will grow even more rapidly than that of whites; by the year 2030, estimates are that they will represent 25% of the older population. Of the elderly population in 1996, 8% were African-American, about 5% Hispanic, 2% Asian or Pacific Islander, and less than 1% were American Indian (American Association of Retired Persons, 1997).

A brief review of available information about drugs other than alcohol follows. *Prescribed medications and over-the-counter medications* are disproportionately used by older people. Considering health status in this age group, that is hardly remarkable. What should be noted, however, is the problem of drug interactions, that is, the interactions of medications with each other and with alcoholic beverages. It has been documented that older people are more likely than younger people to have adverse drug reactions (ADRs). Dosages, too, must be considered because the effect of a drug on older people may not be the same as its effect on younger adults. There is also some information that the elderly are disproportionately users of sedatives/hypnotic.

The use of *nicotine* has dropped among older people as it has among younger adults. The National Center for Health Statistics (1996) noted that the percentage of smokers had dropped from 42% in the 1960's to 25% in 1993. Men are more likely to be smokers than women, although the gender gap has narrowed: in 1993, the percentage of smokers was 13.5% for older men and 10.5% for older women. A study of older people in Massachusetts shows that

those least likely to be smokers were respondents living alone or with their children, those who reported their health as poor or fair, and the frail elderly.

Illegal or street drugs are used very little by elderly people. Occasional use of drugs such as marijuana, cocaine, and heroin does occur, but it is infrequent. A group of elderly heroin addicts who attend methadone maintenance clinics in New York City has been reported (DesJarlais et al., 1985; Pascarelli, 1985) and studied primarily to study the bases for their survival for example, avoidance of violence, attention to clean needles, etc. Barr (1985), treating both aging alcoholics and aging narcotic addicts, commented that, "... if drug addicts survive the risk of violent, death, their medical complications may not be as severe as those of older alcoholics..."

2.1. Alcohol

To what extent are alcoholic beverages used by older people? It has been accepted until recently that the proportion of people who drink moderately (or infrequently) drops with old age. This may be true, but there are a number of reports that question this drop (Glynn et al., 1984; Huffine et al., 1989; Moore et al., 1999). Adams and colleagues (1993) studied alcohol-related hospitalizations of the elderly and found that such hospitalizations are "common." One may conclude that the question of *elderly social usage of alcohol* is not resolved; abuse and dependency may occur less frequently among older adults than among younger ones but that moderate, social usage of alcohol is greater than originally estimated.

The question about the *etiologies of alcohol problems* among the elderly is little discussed and usually, the same theoretical explanations offered for abuse/dependence are offered. An important distinction, relevant to the causes of abuse/dependence is *early versus late onset*. One offered etiology was that late onset was linked to the stresses and hardships of aging; available studies do not, as a rule, support this linkage. Genetics cannot be ruled out because genetic effects do not necessarily appear at birth (McClearn, 1998). Most useful is probably a longitudinal/developmental framework of etiology including physiological, behavioral, and sociocultural variables.

The criteria for the diagnosis of alcoholism, need to be reconsidered for the elderly. They are likely to be retired or unemployed, so that losing time from work may be irrelevant; on the other hand, alcohol-related medical problems are more relevant, and may be the entry into treatment for alcoholism, that is most useful for this age group. A study by Adams et al. (1993) examined alcohol-related hospitalizations, including the records of all hospital inpatient Medicare Part A beneficiaries, 65 and older. The highest rate of such hospitalization was in the 45 to 64-year-old group (94.8 per 10,000 population), and the second highest rate was in the 65+ group (65.1 per 10,000 population). Alcohol-related disorders included alcoholic liver disease, psychoses, cardiomyopathy, gastritis, and polyneuropathy. Cognitive loss is an issue, but a hypothesis about "premature aging," positing premature senescence brought on by heavy

alcohol intake, yielded mixed results. The reversibility of cognitive impairment, usually manifest in short-term memory, nonverbal abstracting, and the ability to process new information, is an interesting research question: many clinicians believe that the impairment is reversible but takes longer with older patients.

The relatively low prevalence of problem drinking among older women is questioned by Wilsnack et al. (1995) who suggest underreporting and the absence of "... the most at-risk or impaired women" from community surveys. Gomberg (1995) presents a few of the gender differences: (1) older male problem drinkers are more likely to be married, divorced, or separated, but older women problem drinkers show a much higher rate of widowhood (true of the population in general); (2) onset is more recent among older women, and they are more likely to have a spouse/lover who is a heavy drinker; (3) women are more likely to be problematic users of prescribed psychoactive drugs; and (4) gender differences appear in the reported effects of alcohol—women state that they become more depressed when drinking, and men report more positive effects. There is a curious contradiction: older male problem drinkers report getting along better with people but have significantly more quarrels with family. Consistent with findings in other age groups, older women problem drinkers' major comorbidity is depressive disorder.

There are fewer research reports about substance problems of the elderly than there are about substance problems and gender or substance problems and ethnicity. Whether this is because the question is a newer one or whether it is due to the more tender years of research personnel is anyone's guess. There is awareness of and interest in training medical students in geriatric medicine (e.g., Mortimer, 2001).

For the interviewees in a telephone survey, aged 61 and older, 69% reported gambling during the past year; only 51.5% had consumed any alcohol during the same period. (It may be of interest to note that a larger proportion of elderly women reported more gambling and a larger proportion of older men report more use of alcohol.) There is a positive correlation between problem drinking and problem gambling, particularly among younger adults. The authors attribute this correlation to "... a tendency to ignore social rules and long-term consequences. Nor is gambling pathology spread evenly in the social classes; minorities and lower income persons have a higher than average prevalence."

It is clear from epidemiological evidence that the percentage of drinkers drops off with old age. This probably is true in the proportion who drink at all and in the lower amounts they drink. But, as has been pointed out (Gomberg, Hegedus, & Zucker, 1998), substance abusers do exist in older age groups. They are, in fact, differentiated in terms of early onset and later onset usage and role of alcohol, as it manifests itself over the life course (Zucker, 1998), and alcohol problems and aging are reviewed in a research monograph published by the U.S. Department of Health and Human Services, edited by Gomberg, Hegedus, and Zucker (1998). The latter includes chapters on basic issues, biological mechanisms, course and consequence treatment, prevention, and, a closing summary chapter on research issues and priorities.

2.2. *Treatments*

In a review of treatment programs for older alcoholics, Atkinson (1995) reviews nontreatment factors that influence outcome: comorbidity, demographics and setting variables, measurement of alcohol consumption, and measuring functional status. Atkinson's review of "mixed age" studies concludes that, "... No study has shown that age confers a special liability for poor treatment outcome" (p. 197). That leaves the question of the benefits of age-specific treatment for older problem drinkers. The consideration of age-specific treatment is based on different age-associated etiologies and risk for relapse; cognitive, social, and value differences; social bonding with age peers; and the appropriateness of some treatment approaches (e.g., routine use of disulfiram). The conclusion: in spite of the limited number of controlled studies, they consistently suggest that age-specific treatment is superior to mixed age treatment.

Several cognitive therapy approaches have been developed for treating alcoholics, and some for specific use with elderly patients (Glantz, 1995). In the first stage, patients try to define their goals and the problems to be overcome, after which individual plans must be developed, including skills training, treatment of comorbid conditions, relapse prevention, etc.

A review of recurring treatment issues by Dupree and Schonfeld (1998) discusses (1) screening and identification; (2) encouragement of voluntary admission; (3) instruments to define person-appropriate interventions; (4) research on effective programs with older alcohol abusers; (5) knowing when discharge is appropriate; and (6) general program issues: age-specific versus mixed age treatment, preferred treatments, social support networks, denial versus confrontation, abstinence versus negotiated treatment goals, dual diagnoses, and assessment of treatment outcome. Dupree and Schonfeld list some conclusions about elderly alcoholism treatment that which have empirical support:

1. Emphasize age-specific group treatment with a supportive approach avoiding confrontation.
2. Focus on negative emotional states and overcoming losses.
3. Rebuild social support network, teaching the skills to rebuild a network.
4. Employ staff experienced and interested in working with older clients.
5. Develop linkage with aging services, medical services, and institutional settings.
6. Develop the pace/content of older person treatment.

Atkinson (1995) makes several recommendations for future research:

1. Determine the characteristics of those elderly alcoholics who need treatment versus those who need simple advice or peer support.
2. Develop elder-specific outcome measures (alcohol consumption and functional status).
3. Study putative age-associated risk factors for relapse (cognitive impairment, depression, chronic illness).

4. Determine the comparative efficacy of cognitive-behavioral therapy for patients randomly assigned to age-specific or mixed groups.
5. Compare the efficacy of age-specific outpatient treatment by individual cognitive-behavioral therapy versus supportive social therapy.
6. Study models for treating comorbidity.
7. Study treatment needs of aging women and minorities.
8. Study older people with active alcohol problems who enter rehabilitation programs with a likelihood of eventual discharge to the community.

What it comes down to is research needed on screening, prevention, development of age-appropriate testing instruments, the efficacy of different treatment approaches, the issue of denial in treatment, study of comorbidity, treatment goals, and assessing treatment outcome.

2.3. Ethnicity

The National Institute on Alcohol Abuse and Alcoholism (1989) published papers on alcohol use among U.S. ethnic minorities. The conference from which these papers are drawn was "... on the epidemiology of alcohol use and abuse among ethnic minority groups." The subheadings are Alcohol Use among Black Americans, among Hispanic-Americans, among American Indians and Alaskan Natives, and among Asian/Pacific-Americans. One recommendation on Black Americans is of interest:

Research on blacks in alcohol treatment programs. Comparatively little research has been done on blacks in formal alcohol, drug and mental health programs. This information is needed to assess community responses with informal and institutional settings to the misuse of alcohol by blacks. Studies should explore factors that enable blacks and other minorities to recover successfully from alcohol dependence. Future studies should also examine the factors that promote abstinence in large segments of the black population and help to explain why blacks, on the average, are significantly younger than whites in treatment. (p. 467)

The Substance Abuse and Mental Health Services Administration (1998) has published a report on the prevalence of substance use among racial/ethnic subgroups, 1991–1993. The highest percentage of heavy alcohol use is by Mexican-Americans, other Hispanics, African-Americans, and Native Americans (Caucasians rank second). Alcohol dependence is ranked high for Native Americans followed by Mexican-Americans, Puerto Ricans, and African-Americans. Other Hispanic groups (e.g., Cubans, Central American Caribbeans, and South Americans) rank lower. It is of interest that the Department of Health and Human Services established an Asian-American and Pacific Islander Initiative in 1997, but its health-related concerns do not include alcohol or substance abuse.

Alcohol studies of ethnics in the 1940s and 1950s was of immigrant groups within the United States—the Irish, the Jews, the Italians, and the Chinese.

In the 1960's, alcohol studies expanded to survey research and was further complicated by the rise of the Black civil rights movement that increased ethnic identifications within America and led to a new interest in the relationship between ethnicity and drinking. Views about "the drunken Indian" were reexamined (e.g., MacAndrew & Edgerton, 1969), and Stivers' (1976) work on Irish-American drinking emphasized the dynamic changes that could occur with new circumstances, that is, Irish-American drinking was quite different from pre-migration drinking in Ireland. Much of the new work was presented by Bennett and Ames (1985) in an edited volume titled, *The American Experience with Alcohol: Contrasting Cultural Perspectives*. The following summarizes the reports of the four federally mandated minorities.

2.3.1. American Indians. Liquor, as part of trade exchanges was established in the eighteenth century. However, one of the major difficulties in describing American Indian patterns (in any area) is the reality of regional, tribal and intratribal variation—they are not a homogeneous ethnic group. Some tribes ban the use of intoxicating beverages, but many more tribes do not. The grievances of Indian tribes about the United States are the grievances of the colonized. There is (1) sacred separation: all things seen as non-Indian are profane and to be discarded; alcohol is the "white man's disease." (2) Profane separation—this involves the misuse of alcoholic beverages in a public context. Laws governing the liquor trade with Indian tribes have a long history. (3) Belief in the Indian as moderate or rational, including the monitoring of one's own drinking behavior. Powwows, in the past, have been occasions for heavy drinking and its social consequences. Currently, public inebriation has been eliminated in part by invoking the notions of sacred versus secular space.

Alcohol abuse is still a major medical/social problem for many tribes. Treatment outcome studies show poor results, presumably because of the cultural bias of existing interventions. What seems to be called for is the integration of more traditional forms of healing practices in programs with many Indian clients (Weibel-Orlando, 1985). Weibel-Orlando describes a number of used treatment modalities: (1) alcoholism as a disease, medical model, influenced by AA; (2) sociopsychanalytical orientation with emphasis on identification and resolution of psychosocial problems; abusive drinking seen as a symptom; (3) assimilative model Indian-staffed and Indian-run, using standard modalities; (4) culture-sensitive model, usually with Indian counselors; group therapy with emphasis on Indian historical/culture themes; (5) syncretic model, incorporating Indian values and ceremonial curing practices into standard alcoholism intervention strategies; and (6) traditional model: traditional or spiritual leaders to combat craving for alcohol, excluding other therapies.

The programs most successful with clients are those that integrate a variety of spiritual elements and activities into their treatment strategies. Sociopolitical changes, for example, the American Indian Movement strongly advocates abstinence from all intoxicants (Weibel-Orlando, 1985).

2.3.2. African-Americans. Herd (1985) makes the point that the universal ambivalence about alcohol in the United States is particularly high among blacks. Two pictures emerge: Urban: indulgent, tolerant attitudes, the great migration north, and the role of black nightclub culture during Prohibition; the other, temperance, allied to the struggle to attain political/social equality. Though they were probably in all-black chapters, many black women were members of the Women's Christian Temperance Union. During the Prohibition years, there were disproportionate deaths and hospital admissions among blacks; black cirrhosis mortality rates rose steeply in the 1950s. Theories about "stress" and response to oppression as explanations for black drinking fail to explain the increase in black alcohol problems since slavery. Herd's view is that black attitudes toward alcoholic beverages are profoundly affected by changes in the larger society and major demographic shifts in the black population.

Gaines (1985) distinguishes between "respectable drinking" (including abstinence, sipping, and weekend drinkers) and problem attitudes about male versus female alcohol use: "...it was considered totally unacceptable for a woman to appear drunk in public..." (p. 183). It would be useful now to explore these dichotomous attitudes among the black middle class and upper middle class, among college students, among black professional women, etc.

The information about black use of alcohol is dynamic and probably changing. Herd (1989), reporting from a 1984 survey, wrote that black and white men had similar drinking patterns, but that women differed. For example half the black women and a third of white women were abstainers—interestingly, they were nearly identical in heaviest drinking. There were age differences, too (which seem to have changed over time): there was less drinking among black adolescents but more heavy/problematic use among middle-aged blacks. The incidence of alcohol-related medical problems, particularly cirrhosis, is very high (interestingly enough, not among those blacks who did not migrate north).

Black culture is "familistic" (Gaines, 1985), and it is difficult for people to seek treatment from "strangers": lack of trust and even danger of crimination and oppression; another theory is etiology based in the person's microsocial world of relatives, lovers, and work. Drinking is a response to frustration or the "blues." Also of concern was the confidentiality of those in treatment and possible gossip about them.

Black culture is not a single entity and some African ancestry, though it may work as a census factor, does not mean one subculture. Black society is a collection of subgroups and subcultures, and it would expedite research on treatment, points of view, efficacy, etc. to include these variations.

2.3.3. Asian-Americans. Kitano et al. (1985) write of the "strong family system" among the Japanese-Americans so that they appear in very low numbers in alcohol treatment programs. In Japan, although drinking is often associated with social problems, it is believed that it is a private matter. Patterned after AA, the All Nippon Sobriety Association Japanese-Americans, like

the other Asian groups in the United States, drink less than white Americans, attributable perhaps to the flushing reflex. That very few Japanese-Americans participate in alcohol is perceived as the social cement that binds people together, but the overt motives for drinking did include alienation and culture clash. Of an estimated 157 Japanese-American alcohol abusers, only 3.1% were admitted to treatment. It would be interesting to explore generational differences: Isei, Nisei, and Sansei.

Alcohol consumption in Chinese folk society is sanctioned for ceremonial or medicinal purposes. Apparently, as depicted in Chinese classical literature, there are two groups of drinkers: the literati or gentry and the elderly for whom drinking is tolerated ostensibly for health reasons. It would be of interest to investigate the gender ratio of drinkers and abstainers among younger and older Chinese-Americans.

2.3.4. Hispanic-Americans. As is true of all other minorities, this is not a homogeneous group but includes Mexicans, Puerto Ricans, Dominicans, Guatemalans, etc. Furthermore, these subgroups bring with them attitudes and customs relating to alcohol. An interview survey indicates (Caetano, 1989) that Mexican-Americans drink more than other subgroups and report more alcohol-related problems. Quantity/frequency of drinking varies within the Hispanic American population by age, income, and education. Of interest is the observation of maintenance of alcohol-related problems by men in their twenties and thirties (unlike the general American population of males in which alcohol-related problems peak in the early years and begin to decline in the thirties). Regardless of the alcohol-related problem examined, Hispanic men in California did not show a decline in problems until the forties. Respondents of all Hispanic subgroups indicated that men in their thirties had more freedom to drink than younger men.

Three Hispanic-American groups in the northeast United States have been studied: Dominicans, Guatemalans, and Puerto Ricans (Gordon, 1985). Dominicans tend to come with their families, and they drink in moderate fashion on Saturday nights with families at social clubs. Guatemalans drink beer heavily through extended weekends. It is of interest that Alcoholics Anonymous is a cultural tradition in Guatemala and in Central America. Puerto Ricans have more fully adopted U.S. drinking customs and when problem drinking appears in a family, they are likely to seek out treatment, probably most often with a pentecostal church. Other Hispanic subgroups reject the pentecostals, and Puerto Ricans vary in their acceptance of AA (in New York City, they were active in AA, but in other northeastern cities, they rejected AA). Another source of alcoholism therapy for Puerto Ricans had been Centros for Espiritismo.

The view that Hispanics do not seek help with alcohol problems means that they do not seek help in formal clinical settings. However, the traditional clinical settings view alcohol problems indigenous treatment do not. Dominicans view heavy drinking as irresponsible and a barrier to progress. Pentecostals see the use of alcohol or drugs as a sin; sins include smoking,

dancing and accepting welfare. Alcohol is not the basic problem; the problem is one of lifestyle and rejection of Jesus. The efficacy of these indigenous treatments has not been studied and is recommended for future research.

In examining recent work, there is an occasional report from Israel, Switzerland, South Africa, or Finland, but the groups most frequently reported on are Mexicans and Mexican-Americans. One such report, gathered in an emergency room (Borges & Cherpitel, 2001), selects items from the Rapid Alcohol Problems Screen (RAPS) and concludes that though RAPS is "a useful tool," it needs more evaluation as a stand-alone instrument..."

Another report focused on Hispanics is a comparison of Cuban, Mexican, and Puerto Rican adolescent drinking patterns (Nielsen & Ford, 2001). Differences are small, but Cubans are less likely than Mexican-Americans to drink frequently, and Puerto Ricans are less likely than Mexican-Americans to drink frequently or frequently/heavily. Subgroup differences among Hispanics apparently manifest themselves early.

Cherpitel (2001) examined the differences in service use between white and Mexican-American DUI arrest, and she notes that the latter are less likely to use the offer of services. The health and social services involved are one of the few places where Mexican-American problem drinkers may be contacted for further treatment, so it behooves such services to reach out to such drinkers.

An analysis of liver cirrhosis mortality data shows results for cirrhosis — (Stinson, Grant, & Dufour, 2001). The highest rate was among white Hispanic men followed by black (non-Hispanic) men and by white (non-Hispanic) men. Among Hispanic descendants, the largest group was of Mexican ancestry; large numbers were born outside the United States and had low educational levels.

These are several studies of American Indians, for example, Navaho and Alaskan natives. A report by Venner and Miller (2001) indicates that the progression of symptoms in problem drinking resembles Jellinek's original group when the group studied does not deviate culturally from Jellinek's original group. A study of gender differences among male/female treated alcohol-dependent Alaskan natives showed that women have more comorbidity, for example, depression and cocaine dependence, also, less marijuana dependence, more pain complaints, more consequences of cocaine dependence, and more medication use. Gender differences must, obviously, be taken into account in treatment planning.

There are two NIAAA publications that relate to racial ethnic minorities. *Alcohol Health and Research World* (1998) has a special edition on alcohol use among U.S. minorities. American Indians: Beauvais (1998) reviews the work and notes that inclusion of native beliefs and approaches may be useful in treating and preventing alcohol problems in this group. African-Americans: Jones-Webb (1998) states that there are consistent findings: more blacks than whites are abstainers, but similar levels of frequent heavy drinking are found in both groups. Hispanic groups compared (Randolph et al., 1998) include Cuban, Mexicans, and Puerto Ricans which show disparities in drinking related to their culture of origin. Asian-Americans have lower rates of use and

alcoholism than other groups (Makimoto, 1998), but the fact is noted that Japanese-Americans show significantly higher heavy drinking rates than Chinese-Americans. There is an interesting finding about these minority groups' use of AA (Tonigan et al., 1998). Hispanics and blacks show lower attendance rates, but Hispanics show "higher level of commitment to AA than do whites."

In NIAAA Research Monograph No.19 (1988) edited by Towle and Harford, findings about cultural influences and drinking patterns of Japanese and Hispanic persons are presented. Cosponsored by the World Health Organization and the Pan American Health Organization, the papers are cross-cultural comparative studies using social epidemiological survey methods. Of interest in the Japanese and Japanese-American samples: the percentage of drinkers was highest among the most educated and those of higher income. In Korea, male heavy drinking is accepted as traditional, but Koreans in California drink less.

References

- Adams, W.L., Yuan, Z., Barboriak, J.J., & Rimm, A.A. (1993). Alcohol related hospitalization of elderly people. *Journal of the American Medical Association* 270 (10), 1222-1225.
- Ahlstrom, S., et al. Gender differences in drinking pattern in nine European countries: Descriptive findings. *Substance Abuse*, 69-81.
- Alcohol Consumption and Problems in European Women. (2001). *Substance Abuse*, 22 (1) 23-81.
- Annis, H.M., & Liban, C.B. (1980). Alcoholism in women: Treatment modalities and outcomes. In O.J. Kalant (ed.), *Alcohol and Drug Problems in Women*. Research Advances in Alcohol and Drug Problems, vol. 5. New York: Plenum, p. 385-422.
- A Profile of Older Americans* (1997). American Association of Retired Persons.
- Are Boys the Weaker Sex? U.S. News and World Report. July 30, 2001, pp. 40-47.
- Atkinson, R.M. (1995). Treatment programs for aging alcoholics: In Beresford, T.P. and Gomberg, E.S.L. (eds.), *Alcohol and Aging*, New York: Oxford University Press, pp. 186-210.
- Beauvais, F. (1998). American Indians and alcohol. *Alcohol Health and Research World*, 22 (4), 253-259.
- Bennett, L.A., & Ames, G.M. (1985). *The American Experience with Alcohol*. NY: Plenum.
- Bloomfield, K., Gmel, G., & Neve, R. et al. Investigating gender convergence in alcohol consumption in Finland, Germany, The Netherlands and Switzerland, *Substance Abuse* 39-54.
- Blume, S.B. (1980). Clinical research, casefinding, diagnosis, treatment and rehabilitation. Research Monograph 1. *Alcohol and Women*. National Institute on Alcohol Abuse and Alcoholism, pp. 121-151.
- Borges, G., & Chertpiel, C.J. (2001). Selection of screening items for alcohol abuse and alcohol dependents among Mexican and Mexican Americans in the Emergency Department. *JSA* 62 (3), 277-285.
- Brennan, P.L., Kagay, C.R., Geppert, J.J. et al. (2001). Elderly medicare inpatients with substance abuse disorders: Characteristics and predictors of hospital admission over a four year period *Journal of Studies on Alcohol* 61, 891-895.
- Bucholz, K.B., Sheline, Y.I., & Helzer, J.E. (1995). The epidemiology of alcohol use, problems and dependence in elders: A review. In Beresford, T.P. and Gomberg, E.S.L. (eds.), *Alcohol and Aging*. New York: Oxford University Press, pp. 19-41.
- Caetano, R. (1989). Drinking patterns and alcohol problems in a national sample of U.S. Hispanics. Research Monograph 18. *Alcohol Use among U.S. Ethnic Minorities*. National Institute on Alcohol Abuse and Alcoholism, pp. 147-162.
- Cherpitel, C.J. (2001)
- Cipriani, F., et al. Alcohol-related mortality in Europe: A tentative analysis, from the EU Project. *Substance Abuse* 55-68.

- DesJarlais, D.C., Joseph, H., & Courtwright, D.F. (1985). Old age and addiction: A study of elderly patients in methadone maintenance treatment. In Gottheil, E., Drule, K.A., Skoloda, T.E., & Waxman, H.M. (eds.), *The Combined Problem of Alcoholism, Drug Addiction and Aging*. Springfield, IL: Charles C. Thomas, pp. 201–209.
- Drugs and Society. (1998). 13 (1,2). *Women and Substance Abuse: Gender and Transparency*.
- Dupree, L.W., & Schonfeld, L. (1998). Older alcohol abusers: Recurring treatment issues. In Research Monograph 33, *Alcohol Problems and Aging*. National Institute on Alcohol Abuse and Alcoholism, pp. 339–358.
- Dupree, L.W., & Schonfeld, L. (1996). Substance Abuse. In Hersen, M. and VanHasselt (eds.), *Psychological Treatment of Older Adults*. New York: Plenum, pp. 281–297.
- Gaines, A.D. (1985). Alcohol cultural conceptions and social behavior among urban Blacks. In L.A. Bennet G.M. Ames (eds.), *The American Experience with Alcohol*. New York: Plenum, pp. 171–197.
- Glantz, M. (1995). Cognitive therapy with elderly alcoholics. In Beresford T.P. and Gomberg, E.S.L. (eds.), *Alcohol and Aging*. New York: Oxford University Press, pp. 211–229.
- Glynn, R.J., Bouchard, G.R., LeCastro, J.S., & Hermos, J.A. (1984). Changes in alcohol consumption behaviors among men in the normative aging study. In Monograph 14, *Nature and Extent of Alcohol Problems among the Elderly*. NIAAA, pp. 101–116.
- Gomberg, E.S.L. (1989a). Alcoholic women in treatment: Early histories and early problem behaviors. *Advances in Alcohol and Substance Abuse* 8 (2), 133–147.
- Gomberg, E.S.L. (1989b). Suicide risk among women with alcohol problems. *American Journal of Public Health* 79 (10), 1363–1365.
- Gomberg, E.S.L. (1991). Women and alcohol: Psychosocial aspects. In Pittman, DJ. and White, H.R. (eds.), *Society, Culture and Drinking Patterns Reexamined*. New Brunswick, NJ: Rutgers Center of Alcohol Studies, pp. 263–284.
- Gomberg, E.S.L. (1995). Older alcoholics: Entry into treatment. In Beresford, T.P., and Gomberg, E.S.L. (eds.), *Alcohol and Aging*. New York: Oxford University Press, pp. 169–185.
- Gomberg, E.S.L., Hegedus, A.M., & Zucker, R.A. (eds.) (1998). Alcohol problems and aging. Research Monog. 33. NIAAA.
- Herd, D. (1985). Ambiguity in Black drinking norms: An ethnohistorical interpretation. In Bennett, L.A. and Ames, G.M. (eds.), *The American Experience with Alcohol*. New York: Plenum, pp. 149–170.
- Herd, D. (1989). The epidemiology of drinking patterns and alcohol-related problems among U.S. Blacks. In Research Monograph 18, *Alcohol Use among U.S. Ethnic Minorities*. NIAAA, pp. 3–50.
- Huffine, C., Folkman, S., & Lazarus, R.S. (1989). Psychoactive drugs, alcohol and stress and coping processes in olderadults. *American Journal of Drug and Alcohol Abuse* 15, 101–110.
- International Council on Alcohol and Addiction, 1988.
- Jones-Webb, R. (1998). Drinking patterns and problems among African-Americans: Recent findings. *Alcohol Health and Research World* 22 (4), 250–254.
- Kitano, H.H.L., & Chi, I. (1989). Asian Americans and alcohol: The Chinese, Japanese, Koreans and Filipinos in Los Angeles. In Research Monograph 18. *Alcohol Use among U.S. Ethnic Minorities*. NIAAA, pp. 375–382.
- Kitano, H.H.L., Hatanaka, H., Young, W., & Sue, S. (1985). Japanese-American drinking patterns. In Bennett, L.A. and Ames, G.M. (eds.) *The American Experience with Alcohol*. New York Plenum, p. 335–358.
- Knibbe, R.A., & Bloomfield, K. Alcohol Consumption estimates in surveys in Europe: Comparability and gender differences. *Substance Abuse* 23–38.
- Lex, B.W. (1994). Women and substance abuse: A general review. In Watson, R.R. (ed.), *Addictive Behavior in Women*. Totowa, NJ: Human Press, pp. 279–328.
- Liebow, E. (1967). *Tally's Corner*. Boston: Little, Brown.
- Lisansky, E.S. (1957). Alcoholism in women: Social and psychological concomitants. I. Social history data. *Quarterly Journal of Studies on Alcohol* 18 (4), 588–623.
- Low, E.A., & Vega, W.A. (2001). Alcohol abuse or dependence among Mexican-American women who report violence. *Alcoholism: Clinical and Experimental Research* 25 (10), 1479–1486.
- MacAndrew, C., & Edgerton, R.B. (1996). *Drunken Comportment: A Social Explanation*. Chicago: Aldine.

- McClearn, G.E. (1998). Genetics, aging and alcohol. In Gomberg, E.S.L., Hegedus, A.M., and Zucker, R. A. (eds.), *Alcohol Problems and Aging*, Research Monograph No. 33. NIAAA, pp. 91–98.
- McCardy, B.S., & Miller, W.R. (1993). *Research on Alcoholics Anonymous. Opportunities and Alternatives*. New Brunswick, NJ: Rutgers Center of Alcohol Studies.
- Maisto, S.A., & Carey, K.B. (1987). Treatment of alcohol abuse. In Nirenberg, T.D. and Maisto, S.A. (eds.), *Developments in the Assessment and Treatment of Addictive Behaviors*. Norwood, NJ: Ablex.
- Marlatt, G.A. (1986). Sex differences in psychosocial alcohol research implications for treatment. In Research Monograph No. 16, *Women and Alcohol: Health Related Issues*. NIAAA, pp. 260–271.
- Martin, S.E., Howard, J.M., Mail, P.D., Hilton, M.E., & Taylor, E.D. (eds.) (1999). *Women and Alcohol: Issues for Prevention Research*, Research Monograph No. 32. National Institute on Alcohol Abuse and Alcoholism.
- Miles, D.R. et al. (2001). Psychopathology in pregnant drug-dependent women with and without comorbid alcohol dependence. *Alcoholism: Clinical and Experimental Research* 25 (7), 1012–1017.
- Moore, A.A., Hays, R.D., Greendale, G.A., Damesyn, M., & Reuben, D.C. (1999). Drinking habits among older persons: Findings from the NHANES I Epidemiologic follow up study (1982–1984). *Journal of the American Geriatrics Society* 47 (4), 412–416.
- Mortimer, J. (2001). Understanding what it means to be older. The newest challenge for young Physicians. *Medicine at Michigan* 3 (3), 44–48.
- National Center for Health Statistics (1996). *Health, United States 1995*. Hyattsville, MD: Public Health Services, p. 173.
- NIAAA (1989). Research Monograph No. 18 *Alcohol Use Among U.S. Ethnic Minorities*, Spiegler, D., Tate, D., Aitken, S., and Cgeutian, C. (eds.).
- Nielsen, A.L., & Ford, J.A. (2001). Drinking patterns among Hispanic adolescents: Results from national household survey. *JSA*, 62 (4), 448–456.
- Pascarelli, E.F. (1985). The elderly in methadone maintenance. In Gottheil, E., Ruley, K.A., Skolda, T.E., and Waxman, H.M. (eds.), *The Combined Problems of Alcoholism, Drug Addiction and Aging*. Charles C. Thomas, Springfield, IL, pp. 210–218.
- Randolph, W.M., Stroup-Benham, C., Black, S.A., & Markides, K.S. (1998). Alcohol use among Cuban-Americans, Mexican-Americans and Puerto Ricans. *Alcohol Health and Research World* 22 (4), 265–269.
- Robinson, E.A.R., Brower K.J., & Gomberg, E.S.L. (2001). Explaining unexpected gender differences in hostility among persons seeking treatment for substance abuse disorders. *Journal of Studies on Alcohol* 62 (5), 667–674.
- SAMHSA (1998). Office of Applied Studies. *Prevalence of Substance, Use among Racial and Ethnic Subgroups in the United States 1991–1993*. Rockville, MD: Department of Health and Human Services.
- Schuckit, M.A., Pitts, F.N., Jr., Reich, T., King, L.J., & Winokur, G. (1969). Alcoholism. I. Two types of alcoholism in women. *Archives of General Psychiatry* 20, 301–306.
- Stinson, F.S., Grant, B.F., & Dufour, M.C. (2001). The critical dimension of ethnicity in liver cirrhosis mortality statistics. *ACER* 24 (8), 1181–1187.
- Stivers, R. (1976). *A Hair of the Dog, Irish Drinking and American Stereotype*. University Park, PA: Pennsylvania State University Press.
- Tonigan, J.S., Connors, G.H., & Miller, W.R. (1998). Special populations Alcoholics Anonymous. *Alcohol Health and Research World* 22 (4), 281–285.
- Towle, L.H., & Harford, T.C. (eds.) (1988). Research Monograph No. 19, *Cultural Influence and Drinking Patterns: A Focus on Hispanic and Japanese Populations*. DHHS.
- Turnbull, J.E. (1988). Primary and secondary alcoholic women. *Social Casework* 69 (5), 290–297.
- Vannicelli, M. (1986). Treatment considerations. In NIAAA Research Monograph 16. *Women and Alcohol: Health-Related Issues*. DHHS, pp. 130–153.
- Venner, K.L., & Miller, W.R. (2001). Progression of alcohol problems in a Navaho sample. *JSA*, 62 (2), 158–165.
- Walitzer, K.S., & Connors, G.J. (1997). Gender and treatment of alcohol related problems. In Wilsnack, R.W. and Wilsnack, S.C. (eds.), *Gender and Alcohol. Individual and Social Perspectives*. New Brunswick, NJ: Rutgers Center of Alcohol Studies, pp. 445–461.

- Wall, J.H. (1937). A study of alcoholism in women. *American Journal of Psychiatry* 93, 943–952.
- Wallerstein, R.S. (1957). *Hospital Treatment of Alcoholism, A Comparative, Experimental Study*, Menninger Clinic Monograph Series No. 11. New York: Basic Books.
- Weibel-Orlando, J. (1985). Indians, ethnicity and alcohol: Contrasting perceptions of the ethnic self and alcohol use. In Bennett, L.A., and Ames, G.M. (eds.), *The American Experience with Alcohol: Contrasting Cultural Perspectives*. New York: Plenum, pp. 201–226.
- Wilsnack, S.C., Vogeltanz, N., Diers, L., & Wilsnack, R. (1995). Drinking and problem drinking in older women. In Beresford, T.P., and Gomberg, E.S.L (eds.), *Alcohol and Aging*. New York: Oxford University Press, pp. 263–292.
- Zucker, R.A. (1999). Alcohol involvement over the life span. 10th Special Report to the U.S. Congress on Alcohol and Health.

Treatment of Tobacco Dependence in Alcoholics

Richard D. Hurt and Christi A. Patten

Abstract. Because of the high morbidity and mortality that alcoholic smokers experience from tobacco-caused diseases, treatment for tobacco dependence among alcoholics is warranted. Much progress has been made during the last decade in addressing tobacco dependence in alcoholism treatment units. Treatment of tobacco dependence in alcoholic smokers does not seem to cause excessive relapse to drinking and, in fact, stopping smoking may enhance abstinence from drinking. Therefore, treatment for alcoholic smokers should take place whenever and wherever the patient comes in contact with the health care system. Because alcoholic smokers as a rule are more dependent on nicotine than their nonalcoholic counterparts, they may need more intensive pharmacotherapy and behavioral therapy. Because many of them have experienced 12-step approaches to recovery, that same technology can be used to initiate and maintain abstinence from tobacco use. Moreover, several pharmacologic options exist to treat tobacco dependence in alcoholic smokers. However, the efficacy of several pharmacologic therapies for alcoholic smokers needs to be tested. In addition, further research is needed on effective treatments for recovering alcoholics of various racial/ethnic backgrounds.

1. Introduction

During the past decade, much progress has been made in bringing tobacco dependence treatment into the mainstream of alcoholism treatment (Hughes, 1996), but much remains to be accomplished. There are many sound scientific reasons to address tobacco dependence among alcoholics, including the reduction of tobacco-caused diseases, which are the leading cause of death for patients previously treated for alcoholism. The observation of successful recovery from alcoholism, but dying from tobacco dependence, has its roots in the very foundation of the 12-Step treatment movement. Bill W., who began his successful recovery from alcoholism in the 1930s and then went on to become

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a cofounder of Alcoholics Anonymous, died of emphysema. A description of Bill W. in his later years tells an incredibly tragic story:

A heavy, sloppy smoker all his life, he developed emphysema in the 1960s. It killed him. He gave his last speech to the international AA convention in Miami in 1970, lifted to the platform in a wheelchair, gasping for breath and sucking oxygen from the tank that was always with him. (Robertson, 1988)

Unfortunately, Bill W.'s story is often repeated today, even though we now have treatments to improve an alcoholic smoker's odds of becoming abstinent from tobacco. As we move forward in the twenty-first century, it seems only logical to place more emphasis on treating tobacco dependence among patients with alcoholism. In this chapter, the importance of addressing tobacco dependence in alcoholism treatment will be highlighted by reviewing the prevalence of tobacco use among alcoholics, studying data on tobacco-caused morbidity and mortality in alcoholics, addressing tobacco dependence in alcoholism treatment units, testing behavioral and pharmacologic treatments for alcoholic smokers, addressing depression in the treatment of alcoholic smokers, and studying the effect of tobacco dependence treatment on alcohol relapse.

2. Prevalence of Smoking in Alcoholics

A considerable decline in the prevalence of smoking among American adults has been observed in the past 30 years (Centers for Disease Control and Prevention, 1999). This measure of progress has not been reflected among smokers with alcohol dependence (Hughes, 1995; Hurt, Dale et al., 1995). The prevalence of smoking among alcoholics and substance abusers is two to three times that of the general population, and they are generally more addicted to nicotine than nonalcoholic smokers (Bobo, 1989; Burling & Ziff, 1988; Joseph, Nichol, Willenbring, Korn, & Lysaght, 1990; Kozlowski et al., 1993; Kozlowski, Jelinek, & Pope, 1986; Kozlowski, Skinner, Kent, & Pope, 1989; Kozlowski, Wilkinson, Skinner, Kent, & Franklin, 1989; Maletzky & Klotter, 1974; Orleans & Hutchinson, 1993). Furthermore, despite the observation that alcoholism is more prevalent among men and there are distinct differences in drinking patterns between men and women alcoholics, the rates of smoking are similar in men and women alcoholics (Miller & Cervantes, 1997). In addition, available research on tobacco use among adolescents treated for substance abuse demonstrate that cigarette smoking is prevalent (>80%) and persists for years following treatment (Myers & Brown, 1994; Myers & Brown, 1997; Myers, Kelly, & Lennox, 1997).

Because of the high prevalence of smoking among alcoholics, it is estimated that alcoholics may constitute as much as 26% of all smokers (DiFranza & Guerrera, 1989). Alcoholic smokers are more tobacco-dependent than non-alcoholic smokers, as indicated by a greater number of cigarettes smoked per day, higher Fagerström Tolerance Questionnaire scores, and high serum nicotine and

cotinine concentrations (Hurt, Dale et al., 1995). Alcoholic smokers may also experience more severe nicotine withdrawal symptoms compared to nonalcoholics (Marks, Hill, Pomerleau, Mudd, & Blow, 1997). Furthermore, nicotine is more reinforcing among patients with a past history of alcoholism than among those without such a history (Hughes, Rose, & Callas, 2000). Moreover, those who are the heaviest smokers are also the heaviest drinkers and vice versa (Craig & Vannatta, 1977), a relationship that is consistent even in the elderly (Mirand & Welte, 1996). This relationship is so strong that intractable heavy smoking has been identified as a predictor of unrecognized alcohol abuse or alcoholism (Hughes, 1996; Vaillant, Schnurr, Baron, & Gerber, 1991).

Studies examining the natural history of smoking among alcoholics indicate that the prevalence rates for smoking in this population do not appear to decline with years of alcohol abstinence (Myers & Brown, 1994; Toneatto, Sobell, Sobell, & Kozlowski, 1995). The small decline in smoking prevalence in alcoholics does not appear to be due to lack of motivation or decreased quit attempts but rather to lack of success among those who try to stop smoking (DiFranza & Guerrera, 1990). In a population-based study, smokers with active alcoholism in the preceding year were 60% less likely to stop smoking than nonalcoholics or recovering alcoholics with more than a year of abstinence from drinking (Breslau, Peterson, Schultz, Andreski, & Chilcoat, 1996). Because the prevalence of smoking is not declining among these smokers at nearly the rate that it is in the general population, the public health burden of smoking among individuals with alcoholism will become even greater (Gritz, 1994).

When abstinence from alcohol is attained without formal treatment, stopping smoking is likely to occur at the same time (Sobell, Sobell, & Toneatto, 1991). Moreover, following inpatient treatment for alcoholism, significant reductions in smoking rates were observed for 45% of 84 patients at 6-months follow-up (Gulliver et al., 2000). Further, abstinence from alcohol and smoking appear to be highly correlated (De Soto, O'Donnell, & De Soto, 1989).

3. Tobacco-Caused Morbidity and Mortality in Alcoholics

It has been known for many years that the number of tobacco-caused deaths is several times higher than those caused by alcohol (Ravenholt, 1984). In the 1990s, tobacco-caused diseases accounted for 19% of all deaths in the United States; alcoholism and other nonnicotine drug dependence accounted for another 6% (McGinnis & Foege, 1993).

The combined use of alcohol and tobacco presents increased health risks from the synergistic effects of these substances, including cancer and cardiovascular disease (Blot et al., 1988; Vaillant et al., 1991). In a study of older alcoholics admitted for inpatient treatment, the frequency of tobacco-caused diseases ranged from cancer of the lung in 2%, emphysema in 23%, to coronary artery disease in 27% (Hurt, Finlayson, Morse, & Davis, 1988). In a retrospective cohort study of 845 Olmsted County, MN, patients who were admitted to an

inpatient addictions unit, there was almost a threefold increased risk of death in these patients compared to that from all-cause mortality in the general population of persons of like age, gender, and calendar year of birth (Hurt et al., 1996). In this study, tobacco-caused diseases accounted for 50.9% of all deaths, and alcohol-caused conditions accounted for 34.1%. The finding that tobacco-caused diseases was the leading cause of death in patients previously treated for alcoholism and/or other nonnicotine drug dependence provides compelling evidence to the addictions treatment community that the treatment of tobacco dependence is imperative in these high-risk patients. In addition, hospitalized patients who are current smokers and have a history of an alcohol problem have markedly lower scores on health status measures of general and mental health (Patten, Schneekloth et al., 2001). Furthermore, current tobacco use and a history of an alcohol problem were each associated with increased psychological distress. Thus, alcoholics represent a particularly important group for tobacco dependence interventions to reduce premature mortality and morbidity.

4. Addressing Tobacco Dependence in Addictions Treatment

Recent efforts have been made to treat nicotine as a drug of dependence in the addictions treatment setting (Joseph et al., 1990). The perception of many patients and addictions treatment staff is that stopping smoking for alcoholics is more difficult than stopping alcohol or other drug use (Kandel, Chen, Warner, Kessler, & Grant, 1997; Kozlowski, Wilkinson et al., 1989). Nonetheless, more than three-quarters of alcoholic smokers who enter an outpatient alcoholism treatment program are willing to consider stopping smoking during or after alcoholism treatment (Ellingstad, Sobell, Sobell, Cleland, & Agrawal, 1999). Interest in stopping smoking is also high among both treatment professionals and patients in inpatient alcoholism treatment settings (Bobo, McIlvain, Gilchrist, & Bowman, 1996). Inpatients with substance dependence are more likely to accept tobacco dependence treatment if they are younger, more addicted to nicotine, have more tobacco-caused health problems, and have a more positive attitude about stopping smoking (Seider, Burling, Gaither, & Thomas, 1996).

Perhaps one of the more contentious issues during the past decade has been incorporating tobacco dependence treatment into the treatment of other addictions. The resistance from the treatment community is reminiscent of the debates that occurred in the mid-1970s when alcoholism treatment centers were confronted with patients who were dependent on alcohol and other drugs. Though similar in some respects, the fear of incorporating tobacco dependence treatment has been more intensive. Furthermore, there has been a call for scientific proof of causing no harm (i.e., not causing relapse to alcohol or other drug use when providing treatment for tobacco dependence) which was not the case when treatment of nonalcohol drugs of dependence was incorporated into the treatment

milieu in the 1970s. Clearly, the excessive mortality from tobacco-caused diseases in patients who have undergone treatment for alcoholism should be compelling enough to bring about the needed changes (Hurt et al., 1996). If addictions treatment providers ignore tobacco dependence in their patients, that would be akin to ignoring other devastating illness such as uncontrolled hypertension or diabetes mellitus in patients undergoing treatment for alcoholism.

One indicator of progress is that several treatment units across the country have become smoke-free, and some have incorporated tobacco dependence treatment into the treatment milieu (Rustin, 1998). Many treatment centers have tried to accomplish this but have failed for a variety of reasons, such as staff resistance or decreasing patient censuses. Others have been able either to overcome these obstacles or have addressed the issue by making tobacco dependence treatment optional. Alternatively, some treatment centers have maintained a smoke-free unit by allowing smokers to leave the unit to smoke. However, simply changing the treatment environment to one that is smoke-free or providing optional tobacco dependence treatment may not increase the likelihood that patients will stop smoking (Patten et al., 1999).

Staff attitudes surrounding the issue of smoke-free policies can be changed, though it takes strong leadership on the part of the program administrators and the development of a plan well in advance of initiating a policy change (Hurt, Croghan, Offord, Eberman, & Morse, 1995) (Rustin, 1998). Such policies, once implemented, seem to have the support of staff (Patten, Martin, & Owen, 1996). There can be short-term (i.e., 3 months) negative effects of implementing a smoke-free policy, such as a decrease in program completion rates, but these trends correct with time. Thus, the goals of becoming smoke-free and incorporating tobacco dependence treatment in alcoholism treatment units can be attained (Rustin, 1998). A methodology to accomplish this has been developed and is being implemented in treatment centers, especially on the East Coast, as a result of training and impetus from the New Jersey program, "Addressing Tobacco in the Treatment of Other Addictions" (Rustin, 1998). Clinicians are being urged to provide nicotine dependence treatment for recovering alcoholics despite the lack of empirical evidence of highly successful treatment efforts (McIlvain, Bobo, Leed-Kelly, & Sitorius, 1998). Nonetheless, much work needs to be done as tobacco dependence, an addiction that has a 50% chance of causing their death, is not addressed for many alcoholics in treatment.

5. Efficacy of Behavioral Treatment for Alcoholic Smokers

Most studies indicate that alcoholics have less success in stopping smoking than nonalcoholics. Among alcoholics undergoing inpatient treatment and receiving a behavioral intervention for smoking, 1-year smoking abstinence rates ranged from 0 to 11% (Bobo, McIlvain, Lando, Walker, & Leed-Kelly, 1998; Burling, Marshall, & Seidner, 1991; Hurt, Eberman, Slade, & Karan, 1993; Joseph et al., 1990). Brief (10–15 minute) individualized counseling sessions (one before

treatment discharge and three telephone counselor sessions postdischarge) produced no difference in inpatient alcoholic smokers in smoking abstinence rates at 12-month follow-up (9%) compared to the no-treatment group (7%). Most studies included low-intensity, tobacco dependence interventions with standard treatment components (e.g., rate fading, motivational interviewing, stimulus control, telephone follow-up) that were not tailored to the needs and issues of alcoholics.

Tailoring interventions to the needs of alcoholics using language and symbols compatible with alcohol treatment may enhance overall outcome (Hurt, Eberman et al., 1993). Using a 12-step approach for tobacco dependence seems to resonate with some recovering alcoholics who have used that approach for their alcoholism (Engelmann, 1989). In one of the few reported prospective trials involving 205 recovering alcoholic smokers, the efficacies of three behavioral smoking interventions were compared (Martin et al., 1997). All participants had at least 3 months of alcohol abstinence prior to smoking treatment. They were randomly assigned to a group-based, 12-week program of behavioral counseling plus exercise, behavioral counseling plus nicotine gum, or standard treatment (American Lung Association 30-day quit program) plus Nicotine Anonymous meetings. The behavioral counseling interventions were developed specifically for recovering alcoholics based on extensive pilot work and incorporated 12-step principles. At posttreatment, the smoking abstinence rates were significantly higher for those in the behavioral counseling plus exercise group compared to the other two treatment arms. The 1-year smoking abstinence rates ranged from 25.7-27.4% and are comparable to those achieved by nonalcoholics. In addition, duration of alcohol abstinence was not associated with the smoking abstinence rate at 1-year. Thus, recovering alcoholics can successfully stop smoking. However, because alcoholics tend to have more severe nicotine dependence than nonalcoholics, low intensity interventions for tobacco dependence are unlikely to yield high rates of abstinence from smoking (Bobo et al., 1998). In fact, in our 7-day intensive residential (i.e., inpatient) treatment program for nicotine dependence at the Mayo Clinic, smokers who are recovering from alcoholism make up more than 30% of the patients (Hays, Wolter et al., 2001). Long-term tobacco abstinence rates are not significantly different between those with or without a past history of alcoholism; thus, residential treatment seems to be equally effective in the two groups of patients.

Few studies have addressed tobacco dependence for adolescent substance abusers (Myers et al., 1997). Using a single group design, a six-session, group-based tobacco dependence intervention for teen inpatients with substance abuse shows promise (Myers, Brown, & Kelly, 2000). The intervention was developed specifically for this population, addressing correlates of adolescent smoking cessation, developmental considerations, and substance abuser-specific factors (Myers, Brown, & Kelly, in press). At 3-months posttreatment, 6 of the 35 adolescents enrolled were abstinent from smoking, and 17 had made a serious quit attempt. The findings were interpreted as providing support for the feasibility and utility of tobacco intervention in the context of adolescent substance abuse treatment.

The optimal timing of tobacco dependence interventions in relation to alcoholism treatment is unknown. In a preliminary study, 29 male inpatients treated for alcoholism were randomized to concurrent smoking cessation treatment (first counseling session began during the inpatient stay) or delayed smoking cessation treatment (first counseling session began 3 weeks after the inpatient stay) (Kalman et al., 2001). The intervention consisted of three 45-minute individual counseling sessions and 8 weeks of 22-mg nicotine patch therapy. No significant differences were detected between the concurrent (19%) or delayed (8%) treatment conditions on the smoking abstinence rates at 1-month follow-up. However, those in concurrent treatment were more likely to enter treatment for tobacco dependence (100%) than those in the delayed treatment (67%), suggesting that early recovery from alcoholism may be an optimal time to engage patients in tobacco dependence treatment. A large, multisite study funded by NIAAA has recently been completed that will show the effect of the timing of tobacco dependence treatment relative to alcohol treatment on smoking abstinence rates (Joseph, Willenbring, Nugent, & Nelson, in press).

The behavioral treatment studies conducted to date have been hampered by a number of methodological limitations, including small sample sizes, lack of adequate controls, and the use of quasi-experimental designs (Sussman, in press). In addition, most studies have included primarily Caucasian participants, and the efficacy of treatments for tobacco dependence among minority alcohol-dependent smokers is virtually unknown.

The latest USPHS Guideline on treatment of tobacco use and dependence (Fiore et al., 2000) concludes that although brief counseling interventions are effective, there is a strong dose response; thus, the effectiveness of individual or group counseling increases with treatment intensity. Specifically, three types of counseling and behavioral therapies were found effective and should be used with all patients attempting to stop using tobacco:

1. Provision of practical counseling (problem solving/skills training).
2. Provision of social support as part of treatment (intratreatment social support).
3. Help in securing social support outside of treatment (extratreatment social support).

These concepts should resonate with alcoholism treatment providers because they are also fundamental to best practices in treating alcoholism. As in nonalcoholic smokers, longer duration of previous smoking abstinence is associated with better tobacco dependence treatment outcomes (Patten, Martin, Calfas, Lento, & Wolter, 2001; Stapleton et al., 1995). It is probable that a longer period of previous abstinence from smoking facilitates the development of coping skills that are useful in subsequent attempts to stop. Thus, treatment providers should capitalize on the smoker's prior experiences and build on any previous successes. However, because of the more severe levels of nicotine dependence and the finding that higher scores on the Fagerström Tolerance

Questionnaire were associated with poorer 1-year smoking abstinence rates in recovering alcoholics (Patten, Martin et al., 2001), treatment success is likely to be enhanced by concurrent pharmacotherapy.

6. Addressing Depression in the Behavioral Treatment of Alcoholic Smokers

An association has been observed between heavy cigarette smoking and a lifetime history of major depression (Breslau, Kilbey, & Andreski, 1993). Numerous studies indicate that a history of major depression is related to failure of tobacco dependence treatment and relapse to smoking (Covey, Glassman, & Stetner, 1990; Glassman et al., 1988, 1990). The magnitude of the relationship between smoking and a history of depression is large and is independent of the effects of sociodemographic characteristics, current depression, and other psychiatric disorders (Breslau, Kilbey, & Andreski, 1991). Although several mechanisms have been postulated, the causal nature of the relationship between smoking and major depression is not fully understood (Choi, Patten, Gillin, Kaplan, & Pierce, 1997; Kendler et al., 1993). However, there is evidence of a biological commonality among tobacco use, alcoholism, drug dependence, and depression, because early onset of regular tobacco use is predictive of the other three (Hanna & Grant, 1999).

The observed concordance between alcohol dependence and major depression (Kessler et al., 1996; Regier et al., 1990; Schuckit, 1986) suggests that individuals with both disorders may represent a population of especially treatment-resistant smokers. This comorbidity is illustrated by a study in which almost 40% of abstinent alcoholics enrolled in a tobacco dependence treatment program met lifetime criteria for major depression independent of their alcohol use (Covey, Glassman, Stetner, & Becker, 1993). Other studies have confirmed this finding; more than one-third of abstinent alcoholics who volunteer for tobacco dependence treatment meet lifetime criteria for history of major depression (Patten, Martin, Myers, Calfas, & Williams, 1998). These observations were made using the DSM-III-R criteria for major depression along with the requirement that the depressive episode occurred either before the onset of the first life problem related to alcohol or during a period of abstinence that lasted 3 months or more (Schuckit, 1986). Moreover, abstinent alcoholics with a history of major depression report higher baseline levels of negative affect (Patten et al., 1998) and may have diminished success in stopping smoking (Covey et al., 1993; Covey, Hughes, Glassman, Blazer, & George, 1994), compared to those without such a history. Thus, treatments that address mood regulation may be effective as additive components of tobacco dependence interventions for alcoholic smokers.

In a preliminary study, the efficacy of a mood management intervention for smokers with past histories of both alcohol dependence and major depression was examined (Patten et al., 1998). Participants with at least 3 months of

alcohol abstinence were enrolled and randomly assigned to a 12-week, group-based program of behavioral counseling alone or behavioral counseling plus mood management intervention. The mood management intervention included cognitive-behavioral strategies found effective in treating depression. At 1-year, the smoking abstinence rates were significantly higher for those in the mood management condition than for behavioral counseling alone (46% vs. 12%). In addition, mood management intervention appears to be effective for alcoholic smokers with high levels of current depressive symptoms, independent of a past history of major depression (Patten, Drews, Myers, Martin, & Wolter, *in press*). A larger clinical trial funded by NIAAA examining the efficacy of mood management intervention for recovering alcoholic smokers with past histories of depression is currently underway.

7. Effect of Tobacco Dependence Treatment on Alcohol Relapse

A growing number of studies indicate that treating tobacco dependence in alcoholic smokers does not adversely affect the outcome of alcohol and drug dependence treatment (Bobo et al., 1998; Bobo, Schilling, Gilchrist, & Schinke, 1986; Hurt, Eberman et al., 1994; Myers et al., 2000; Sobell, Sobell, & Kozlowski, 1995; Toneatto et al., 1995). It was shown that the relapse rate to alcohol or drugs was only 4% among the 205 participants during the 12-months following tobacco dependence treatment (Martin et al., 1997). Other studies conducted with recovering alcoholic smokers have reported alcohol relapse rates of approximately 6% following intervention for tobacco dependence (Novy, Hughes, Jensen, Hatsukami, & Huston, 1999; Patten et al., 1998). Alcoholic inpatients who received a smoking intervention were more likely to be abstinent from alcohol at 6-month follow-up, compared to the no-treatment control group (Bobo et al., 1998). However, most studies have not been designed to test the effects of tobacco dependence treatment on alcohol and drug recovery, had small samples, had few subjects who stopped smoking, and were subject to a variety of sampling biases or other methodological limitations such as lack of biochemical verification of alcohol abstinence.

In nontreatment studies, some reports indicate better drinking outcomes among alcoholics who stopped smoking than among those who did not (Bobo, 1989; Bobo et al., 1986; Miller, Hedrick, & Taylor, 1983; Sobell & Sobell, 1993). Conversely, cigarette smokers treated for alcohol dependence had better alcohol use outcomes at 12-month follow-up than ex-smokers or nonsmokers (Toneatto et al., 1995). Moreover, an epidemiological study of male veterans found that abstinence from smoking was associated with an increase in alcohol consumption (Carmelli, Swan, & Robinette, 1993). However, in the general population, the effects of smoking abstinence on levels of alcohol consumption are also inconsistent (Carmelli et al., 1993; Zimmerman, Warheit, Ulcrich, & Auth, 1990).

The development of skills for managing high-risk situations for smoking relapse may generalize to other behavioral domains such as successful

maintenance of alcohol abstinence (Burling, Ramsey, Seidner, & Kondo, 1997; Burling, Seidner, & Ramsey, 1997; Miller et al., 1983). Conversely, smoking has been reported by alcoholics in treatment as a coping response to urges to drink (Colby et al., 1994). A recent laboratory-based study of alcoholic smokers admitted for inpatient addictions treatment (Gulliver et al., 2000) found that urges to smoke and urges to drink were related in the presence of neutral or alcoholic beverage cues and that alcoholics reported stronger urges to smoke when confronted with alcohol cues than when exposed to a neutral beverage. Moreover, at 6-month follow-up, those who relapsed to drinking and smoked more cigarettes per day drank less frequently than those who smoked fewer cigarettes per day. The authors propose that when returning to drinking, those who smoked cigarettes more were better able to restrain their frequency of drinking by using smoking as a coping tool. In another laboratory-based experiment in alcoholic men, exposure to alcohol cues resulted in greater self-reported urges to drink and smoke but did not actually affect the topography of smoking behavior (Rohsenow et al., 1997).

There are few data on the optimal timing of tobacco dependence treatment in relation to duration of alcohol abstinence. Two prospective trials enrolled recovering alcoholics with at least 3 months of alcohol abstinence and found no adverse effects of participation in smoking cessation treatment on abstinence from alcohol (Martin et al., 1997; Patten et al., 1998). Interestingly, it has been reported that more participants receiving delayed tobacco dependence treatment (55%) relapsed to alcohol at 20 weeks following admission for inpatient alcoholism treatment than those receiving concurrent tobacco dependence treatment (20%) (Kalman et al., 2001).

The USPHS Guideline (Fiore et al., 2000) concludes that intervention for alcoholic smokers does not interfere with recovery from alcoholism and that treatment for tobacco dependence should be conveniently delivered within the context of addictions treatment programs. The Guideline further states that treatment of tobacco dependence can be provided concurrent with treating patients for alcohol and other drug dependence, citing the lack of evidence that such patients relapse to alcohol or other drugs when they stop smoking.

8. Pharmacologic Treatment of Tobacco Dependence in Alcoholics

8.1. First-Line Pharmacotherapy

Generally, the most effective tobacco dependence treatment programs combine pharmacologic and behavioral therapy, though pharmacotherapy for nonalcoholic smokers has been shown effective with minimal behavioral therapy (Fiore et al., 2000). The USPHS Guideline on treatment of tobacco use and dependence recognized five first-line medications (nicotine gum, nicotine patches, nicotine nasal spray, nicotine vapor inhaler, and bupropion) and two

second-line medications (nortriptyline and clonidine) (Fiore et al., 2000). The guideline recommends that, except in the presence of contraindications, all patients attempting to stop smoking should use an effective pharmacotherapy. What follows covers some of the basic information about the five first-line and two second-line pharmacotherapies that are effective in treating tobacco dependence (Fiore et al., 2000) but also extends standard treatment to what might be needed to more effectively treat alcoholic smokers.

8.1.1. Nicotine Replacement Therapy. Meta-analyses of double-blind, placebo-controlled trials indicate that nicotine replacement therapy doubles or triples smoking abstinence rates compared to placebo, especially when paired with behavioral intervention (Fiore, Smith, Jorenby, & Baker, 1994). There is similar efficacy in the general population of smokers for all of the nicotine replacement products (nicotine gum, nasal spray, patches, or inhaler) (Hajek et al., 1999). Though nicotine replacement therapy has been available for many years, very few prospective trials have been performed in alcoholics.

8.1.1.1. Nicotine Patch. Nicotine patch therapy delivers a steady dose of nicotine for 16–24 hours and has become a mainstay for treating tobacco dependence. The once daily dosing requires little effort on the part of the smoker, resulting in high compliance rates. Nicotine patches are available as over-the-counter products in doses of 7, 11, 14, 21, and 22 mg that deliver nicotine for 24 hours, and in a 15-mg size that delivers nicotine for 16 hours. In almost every randomized clinical trial performed to date, the nicotine patch has proven significantly more effective than placebo, usually with a doubling of the stop rate. Standard dose nicotine patch therapy begins with a dose of 21, 22 mg/24 hours or 15 mg/16 hours. Most patients continue this dose for several weeks before tapering the dose during a period of a few weeks. The exact length of treatment will vary and should be individualized to meet the patient's needs. Standard doses of nicotine patch therapy are not effective in all smokers. In fact, it has been shown that a standard dose (22 mg per 24 hours) of nicotine patch therapy achieves a median serum cotinine concentration of only 54% of the cotinine concentration while the smoker is smoking (Dale et al., 1995; Hurt, Dale et al., 1993). Smokers with lower baseline cotinine concentrations have higher smoking abstinence rates when using standard dose nicotine patch therapy, suggesting that their nicotine replacement needs are more adequately met than those with higher baseline serum cotinine concentrations (Hurt, Dale et al., 1994; Paoletti et al., 1996).

A few studies have examined the effectiveness of nicotine patch therapy for alcoholics. In a post hoc analysis of standard dose nicotine patch therapy (22 mg/24 hours), it was found that though abstinent alcoholics achieved an initial smoking abstinence rate of 46% following nicotine patch therapy, this dropped to 0% at 1-year follow-up (Hurt, Dale et al., 1995). Recovering alcoholics were heavier smokers, had higher baseline (while smoking) serum nicotine and cotinine levels, and higher Fagerström Tolerance Questionnaire scores, all indicating a higher level of nicotine dependence, compared to nonalcoholics.

In an open-label trial of nicotine patch therapy, one-quarter of smokers entering an inpatient alcohol and drug treatment unit elected to attempt to stop smoking during their inpatient stay (Saxon, McGuffin, & Walker, 1997), but only 14% reported abstinence from smoking at 21 days, and 10% were abstinent from smoking at 6 weeks. In 117 recovering alcoholic smokers with at least 30 days of alcohol abstinence (average duration was 4.7 years) randomly assigned to a 21-mg/d dose of nicotine patch or placebo, the end of treatment smoking abstinence rates were not statistically different (37% and 26%, respectively) (Novy et al., 1999). Surprisingly, in smokers receiving nicotine patch therapy, recovering alcoholics with at least 1 year of alcohol abstinence had more difficulty in stopping smoking than current alcoholics or nonalcoholics; 6-month cessation rates were 15, 25, and 28%, respectively (Hays et al., 1999).

Though nicotine replacement may be effective in alcoholics, underdosing with standard doses is likely to occur because serum cotinine levels while smoking are significantly higher in active or abstinent alcoholics compared to nonalcoholics (Hurt, Dale et al., 1995; Keenan, Hatsukami, Pickens, Gust, & Strelow, 1990). Thus, tailored nicotine replacement therapy using higher than usual doses or combinations of nicotine replacement products may be necessary to adequately treat alcoholic smokers.

Because of the observation that many people are underdosed using standard nicotine patch doses, trials have been performed among nonalcoholics using higher doses to increase the efficacy of this treatment. Nicotine patch therapy using two 22-mg/24 h patches has been shown safe and well tolerated in heavy smokers, which again is most often the case in alcoholic smokers (Dale et al., 1995; Fredrickson et al., 1995). Short courses of nicotine patch therapy up to 63 mg/d caused no short-term adverse effects on the cardiovascular system (Zevin, Jacob, & Benowitz, 1998). Higher percentage replacement, it has been shown, reduces nicotine withdrawal symptoms (Dale et al., 1995), but the efficacy of such an approach for long-term smoking abstinence has not been completely established (Dale et al., 1995; Hughes et al., 1999; Jorenby et al., 1995; Paoletti et al., 1996; Sachs, Benowitz, Bostrom, & Hansen, 1995; Tonnesen et al., 1999). However, use of higher doses of nicotine patch therapy (i.e., more than one patch at a time) may be appropriate for smokers who previously failed standard dose patch therapy or for those whose nicotine withdrawal symptoms were not adequately relieved with standard therapy (Hughes, 1995).

Using the concept of therapeutic drug monitoring, serum cotinine concentrations can be used to tailor the nicotine replacement dose so that it approximates 100% replacement. A baseline serum cotinine concentration is obtained while smokers are smoking their usual number of cigarettes. An initial nicotine patch dose based on the serum cotinine concentration or cigarettes per day is prescribed, and after reaching steady state (> 3 days of nicotine patch therapy and not smoking), the serum cotinine concentration is rechecked. The replacement dose can then be adjusted according to the steady state cotinine concentration. The percent replacement for a given dose of nicotine patch therapy can

be expressed as follows:

$$\text{Percent replacement} = \frac{\text{steady-state blood cotinine}}{\text{baseline blood cotinine}} \times 100.$$

Table 1 shows the recommended initial dose of nicotine patch therapy based on serum cotinine concentrations (Dale et al., 1995).

Individualizing the nicotine patch dose is warranted because of the interindividual variability of baseline nicotine and cotinine concentrations among individuals who smoke a similar number of cigarettes per day. There also is interindividual variability of steady-state blood concentrations while receiving nicotine patch therapy during abstinence from smoking (Dale et al., 1995; Hurt et al., 1992). Serum cotinine is the test of choice for calculating the percentage replacement, even though urine nicotine or cotinine can be used (Lawson et al., 1998a,b). Serum cotinine concentrations can be drawn at any time of the day for this assessment (Lawson et al., 1998a).

If serum cotinine concentrations are not available or feasible for collection, the replacement dose can be estimated based on the smoking rate. Table 2 shows the initial nicotine patch dose based on the number of cigarettes smoked per day. It has been shown that the smoking rate correlates with the serum cotinine concentrations given in Table 2 (Dale et al., 1995; Lawson et al., 1998a).

Smoking abstinence during the first 2 weeks of patch therapy is highly predictive of long-term smoking abstinence in nonalcoholics, and there is no biological reason why this might be different in alcoholic smokers (Hurt, Dale et al., 1994; Kenford et al., 1994). Thus, it is imperative that the patient have a follow-up visit or a telephone counseling session within the first 2 weeks to determine

Table 1. Nicotine Patch Dose Based on Baseline (while smoking) Serum Cotinine Concentration

Cotinine	Nicotine Patch Dose
< 200 ng/mL	14–22 mg/d
200–300 ng/mL	22–44 mg/d
> 300 ng/mL	≥ 44 mg/d

Table 2. Nicotine Patch Dose Based on Smoking Rate

Number of Cigarettes per Day	Nicotine Patch Dose ^a
< 10	7–14 mg/d
10–20	14–22 mg/d
21–40	22–44 mg/d
> 40	44+ mg/d

^aNicotine patches are available in the following doses: 7, 11, 14, 15, 21, and 22 mg.

the adequacy of withdrawal symptom relief and how well the patient is maintaining smoking abstinence. Relief of nicotine withdrawal symptoms such as irritability, anxiety, loss of concentration, or cravings can be used to gauge adequacy of nicotine replacement, and the dose can be adjusted upward if nicotine withdrawal persists. If the patient continues to smoke during the first 2 weeks of nicotine patch therapy, the treatment must be changed either by adding additional pharmacotherapy (increasing the dose or adding a different medication) or intensifying the behavioral counseling. Though available nicotine patches have quite comparable pharmacokinetic profiles, there are differences among brands that could lead to higher percentage replacement from one brand to another (Gariti et al., 1999). Thus, measuring serum cotinine is a more accurate way of assessing the adequacy of nicotine replacement and avoiding underreplacement. Most patients will use the nicotine patch for 4–8 weeks, but it is safe to use longer if needed to maintain abstinence from smoking. The optimal length of treatment has not been determined.

Few studies (Kalman et al., 2001; Novy et al., 1999) of the nicotine patch have focused solely on alcoholics, though one did enroll nonalcoholics, recovering alcoholics, and active alcoholics (Hays et al., 1999). Importantly, the rate of relapse to smoking in recovering alcoholics initially abstinent with nicotine patch therapy is very high, posing the prospect of using nicotine patch therapy longer in alcoholic smokers (Hurt, Dale et al., 1995).

8.1.1.2. Nicotine Gum. Nicotine gum is available as an over-the-counter product in doses of 2 and 4 mg. Venous serum nicotine concentrations achieved by nicotine gum are relatively low, compared to those produced by smoking cigarettes (Russell, Raw, & Jarvis, 1980). Nonetheless, nicotine gum is effective for tobacco dependence treatment. The 4-mg dose is more effective in smokers who are more dependent (Glover et al., 1996; Sachs, 1995) and is recommended for those who smoke ≥ 25 cigarettes per day, which is most often the case among alcoholic smokers. Nicotine gum can be combined with other nicotine or nonnicotine pharmacotherapies. No studies have been designed to test the efficacy of nicotine gum in alcoholics. A post hoc analysis of nicotine gum studies revealed that smokers with a history of alcohol or other drug problems were less likely to be abstinent from smoking at 1-year follow-up, compared to those with no such history (Hughes, 1993).

8.1.1.3. Nicotine Nasal Spray. Nicotine nasal spray delivers nicotine directly to the nasal mucosa and has been found effective in randomized clinical trials (Schneider et al., 1995). This device delivers nicotine more rapidly than other nicotine replacement products and reduces withdrawal symptoms more quickly than nicotine gum (Hurt et al., 1998; Schneider, Lunell, Olmstead, & Fagerström, 1996). Each spray contains 0.5 mg of nicotine, and one dose is one spray in each nostril (a total of 1 mg). Recommended dosing is one to two doses per hour, not to exceed five doses per hour or 40 doses per day. The nicotine nasal spray can be used as a single agent, but it is more often used in combination with other nicotine replacement products or with bupropion. Its more rapid relief of nicotine withdrawal symptoms allows using it to extinguish

acute urges to smoke. There was early concern that the nicotine nasal spray could have long-term abuse liability (Sutherland et al., 1992); more recent information indicates that the potential for abuse is low (Schuh, Schuh, Henningfield, & Stitzer, 1997). No studies have tested the efficacy of the nicotine nasal spray to help alcoholics stop smoking.

8.1.1.4. Nicotine Inhaler. The nicotine vapor inhaler has been shown effective in placebo-controlled trials (Leischow et al., 1996). This device is a plastic holder into which a cartridge containing a cotton plug impregnated with 10 mg of nicotine is inserted. It delivers nicotine vapor to the oral mucosa where it is absorbed. Little if any of the nicotine reaches the pulmonary alveoli even with attempted deep inhalations. Thus, it does not provide high arterial concentrations of nicotine like cigarettes (Bergström, Nordberg, Lunell, Antoni, & Långström, 1995; Lunell, Bergström, Antoni, Långström, & Nordberg, 1996; Lunell, Molander, Ekberg, & Wahren, 2000). When used as a single therapy, efficacy is increased when more than six cartridges per day are used. The nicotine vapor inhaler is a relatively low delivery device, thus is most often used in combination with other nicotine replacement products and/or bupropion. The nicotine inhaler has not been tested for efficacy in alcoholic smokers.

8.1.2. Bupropion. Bupropion is a monocyclic antidepressant which is an inhibitor of the reuptake of norepinephrine and dopamine (Ascher et al., 1995). Dopamine release in the mesolimbic system and the nucleus accumbens is thought to be the basis for the reinforcing properties of nicotine and other drugs of addiction (Clarke, 1993; DiChiara & Imperato, 1988; Pontieri, Tanda, Orzi, & DiChiara, 1996). It is hypothesized that the efficacy of bupropion for treating tobacco dependence stems from its dopaminergic activity on the pleasure and reward pathways in the mesolimbic system and nucleus accumbens rather than its antidepressant activity. Recently, it has also been shown that bupropion is a competitive inhibitor of nicotinic acetylcholine receptors (Fryer & Lukas, 1999; Slemmer, Martin, & Damaj, in press). Thus, its mechanism of action in treating smokers is likely multifactorial.

Sustained-release bupropion has been shown, to be effective in a double-blind, placebo-controlled, dose-response study (Hurt et al., 1997). In addition to efficacy for smoking abstinence, there was an attenuation of weight gain during the treatment period for those who were continuously abstinent from smoking while receiving the 300-mg per day dose. The attenuation of weight gain did not persist at 1-year follow-up. Bupropion is equally effective in smokers with or without a past history of major depression or alcoholism (Hayford et al., 1999). Treatment with bupropion alone or in combination with the nicotine patch resulted in a significantly higher 1-year rate of smoking abstinence than the use of either the nicotine patch alone or placebo (Jorenby et al., 1999). Abstinence rates were higher with combination therapy than with bupropion alone, but this difference was not statistically significant.

Treatment with bupropion should be initiated about 1 week before the patient's stop date, at an initial dose of 150 mg per day for 3 days, then 150 mg

twice daily. The usual length of treatment is 6–12 weeks, but bupropion can be used safely much longer. A small risk (0.1%) of seizure is associated with bupropion (Johnston et al., 1991). Therefore, it is contraindicated in patients with a history of seizures or serious head trauma such as a skull fracture or a prolonged loss of consciousness. Obviously, in alcoholic smokers, a careful history must be taken to assess for seizure potential. Though not usually related to CNS structural changes, previous alcohol withdrawal seizures in a patient might preclude the use of bupropion. Bupropion is also contraindicated in patients with anorexia nervosa or bulimia. Recent reports from the U.S. Food and Drug Administration suggest that treatment-emergent hypertension may become evident during treatment with bupropion, especially when it is used in combination with nicotine patch therapy. Periodic blood pressure measurements during treatment are advised.

Bupropion has also been tested as a pharmacological relapse prevention treatment (Hays, Hurt et al., 2001). Smoking abstinence rates were significantly higher in the bupropion group compared to placebo at the end of 1 year of medication therapy but were not different a year after the medication was discontinued. As with the dose-response study, the extended use of bupropion for relapse prevention is effective for smokers with or without a past history of depression or alcoholism. But there was inadequate power to draw the same conclusion regarding a history of alcoholism. (Cox et al., in press). It has been theorized but not proven that pharmacologic adjuncts that attenuate depressive symptoms may be particularly effective in preventing smoking relapse in recovering alcoholics. No studies to date have focused solely on alcoholic smokers. However, in a current trial funded by NIAAA, we have enrolled 192 recovering alcoholic smokers in a study designed to test the efficacy of bupropion for smoking relapse prevention.

Because of the high prevalence of a past history of depression in alcoholic smokers, clinicians will often encounter an alcoholic smoker who wants to stop smoking but is already receiving treatment with an antidepressant. There is no drug/drug interaction to preclude the use of bupropion with either selective serotonin reuptake inhibitors or tricyclic antidepressants. Thus, it is usually preferable to add bupropion to a selective serotonin reuptake inhibitor rather than to discontinue that medication and use only bupropion. Though one study showed no serious adverse effects in using bupropion to treat smokers who were already receiving an SSRI (Chengappa et al., in press), patients who receive two antidepressants should be monitored carefully.

8.2. Second-Line Pharmacotherapy

8.2.1. Nortriptyline. Nortriptyline is a tricyclic antidepressant that is recommended as a second-line drug for helping smokers to stop smoking (Fiore et al., 2000). There have been two randomized clinical trials that show a significant effect with active nortriptyline compared to placebo (Hall et al., 1998; Prochazka et al., 1998). In these studies, the maximal dose range was 75–100 mg per day, and the length of treatment was 8–12 weeks. As with bupropion, nortriptyline

produced higher smoking abstinence rates than placebo, independent of a past history of depression. Increases in negative affect after quitting smoking were attenuated by nortriptyline (Hall et al., 1998). Nortriptyline has not been tested for efficacy in alcoholic smokers.

8.2.2. Clonidine. Clonidine is a centrally acting alpha-agonist that can be used as a second-line drug (Fiore et al., 2000). Though available in oral or transdermal form, the transdermal form is easier to use with a recommended dose of 0.2 mg/d for 3 to 10 weeks. The clonidine patch should be initiated a week before the patient's stop date and changed weekly thereafter.

8.3. Combination Pharmacotherapy

There have been a few studies performed using combinations of nicotine replacement therapy and one study using the combination of nicotine patch therapy and bupropion. The U.S. Public Health Service Guideline recommends that combining the nicotine patch with a self-administered form of nicotine replacement therapy, either the nicotine gum or nicotine nasal spray, is more effective than a single form of nicotine replacement. This approach should be encouraged if a patient is unable to stop smoking using a single type of first-line pharmacotherapy or if patients have more severe tobacco dependence. It is unknown whether the superiority of combination therapy is due to the use of two types of delivery systems or because two delivery systems produce higher serum nicotine concentrations than produced by one medication. It has been shown that nicotine patch therapy combined with nicotine gum, reduces nicotine withdrawal symptoms (Fagerström, Schneider, & Lunell, 1993) and improves abstinence outcomes, compared with placebo gum and nicotine patch therapy (Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson, 1995). Nicotine patch therapy for 5 months combined with nicotine nasal spray for 1 year produced higher smoking abstinence rates than nicotine patch therapy with placebo nasal spray (Blondal, Gudmundsson, Olafsdottir, Gustavsson, & Westin, 1999). Treatment with the nicotine vapor inhaler plus nicotine patch also significantly increases smoking abstinence rates beyond those with the inhaler plus placebo patch (Bohadana, Nilsson, Rasmussen, & Martinet, 2000). As mentioned earlier, nicotine patch therapy combined with bupropion was not significantly more effective than bupropion (Jorenby et al., 1999).

8.4. Unproven Pharmacotherapies for Tobacco Dependence

A large clinical trial using fluoxetine in smokers trying to stop has been performed. The results of the main effect have not been reported presumably because no significant efficacy was found. In 25 alcoholic smokers with current major depression, fluoxetine did reduce the smoking rate by 27%, but this was not significantly different from those receiving placebo (Cornelius et al., 1997). In addition, the serotonin uptake inhibitors zimeldine and citalopram had no

effect on smoking abstinence in a pilot study involving 22 male alcoholics (Sellers, Naranjo, & Kadlec, 1987). In two small studies, it has been shown that mecamylamine in combination with nicotine patch therapy has potential efficacy, but a larger randomized clinical trial has been completed which, on preliminary analysis, did not show efficacy (Rose et al., 1994; Rose, Westman, & Behm, 1996). Neither naltrexone nor levodopa show evidence of efficacy despite theoretical reasons to believe they might be effective in helping smokers to stop smoking (Covey, Glassman, & Stetner, 1999; Hurt et al., 2000; Wong et al., 1999). Naltrexone in combination with nicotine patch therapy reportedly reduces the urge to smoke and nicotine withdrawal symptoms in smokers exposed to smoking cues (Hutchison et al., 1999).

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References

- Ascher, J.A., Cole, J.O., Colin, J.N., Feighner, J.P., Ferris, R.M., Fibiger, H.C., Golden, R.N., Martin, P., Potter, W.Z., Richelson, E., & Sulser, F. (1995). Bupropion: A review of its mechanism of anti-depressant activity. *Journal of Clinical Psychiatry* 56(9), 395-401.
- Bergström, M., Nordberg, A., Lunell, E., Antoni, G., & Långström, B. (1995). Regional deposition of inhaled ¹¹C-nicotine vapor in the human airway as visualized by positron emission tomography. *Clinical Pharmacology and Therapeutics* 57(3), 309-317.
- Blondal, T., Gudmundsson, L.J., Olafsdottir, I., Gustavsson, G., & Westin, A. (1999). Nicotine nasal spray with nicotine patch for smoking cessation: Randomized trial with six year follow up. *British Medical Journal* 318, 285-288.
- Blot, W.J., McLaughlin, J.K., Winn, D.M., Austin, D.F., Greenberg, R.S., Preston-Martin, S., Bernstein, L., Schnoenberg, J.B., Sternhagen, A., & Faurmeni, J.F. (1988). Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research* 48, 3283-3287.
- Bobo, J.K. (1989). Nicotine dependence and alcoholism epidemiology and treatment. *Journal of Psychoactive Drugs* 21, 323-329.
- Bobo, J.K., McIlvain, H.E., Gilchrist, L.D., & Bowman, A. (1996). Nicotine dependence and intentions to quit smoking in three samples of male and female recovering alcoholics and problem drinkers. *Substance Use and Misuse* 31, 17-33.
- Bobo, J.K., McIlvain, H.E., Lando, H.A., Walker, R.D., & Leed-Kelly, A. (1998). Effect of smoking cessation counseling on recovery from alcoholism: Findings from a randomized community intervention trial. *Addiction* 93, 877-887.
- Bobo, J.K., Schilling, R.F., Gilchrist, L.D., & Schinke, S.P. (1986). The double triumph: Sustained sobriety and successful cigarette smoking cessation. *Journal of Substance Abuse Treatment* 3, 21-35.
- Bohadana, A., Nilsson, F., Rasmussen, T., & Martinet, Y. (2000). Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation. A randomized, double-blind, placebo-controlled trial. *Archives of Internal Medicine* 160, 3128-3134.
- Breslau, N., Kilbey, M., & Andreski, P. (1991). Nicotine dependence, major depression, and anxiety in young adults. *Archives of General Psychiatry* 48, 1069-1074.
- Breslau, N., Kilbey, M., & Andreski, P. (1993). Nicotine dependence and major depression. New evidence from a prospective investigation. *Archives of General Psychiatry* 50, 31-35.

- Breslau, N., Peterson, E., Schultz, L., Andreski, P., & Chilcoat, H. (1996). Are smokers with alcohol disorders less likely to quit? *American Journal of Public Health* 86(7), 985-990.
- Burling, T.A., Marshall, G.D., & Seidner, A.L. (1991). Smoking cessation for substance abuse inpatients. *Journal of Substance Abuse* 3, 269-276.
- Burling, T.A., Ramsey, T.G., Seidner, A.L., & Kondo, C.S. (1997). Issues related to smoking cessation among substance abusers. *Journal of Substance Abuse* 9, 27-40.
- Burling, T.A., Seidner, A.L., & Ramsey, T. (1997). A controlled trial of stop-smoking treatment for drug/alcohol dependent patients. Paper presented at the *Annual Meeting of the Society of Behavioral Medicine*, San Francisco, CA.
- Burling, T.A., & Ziff, D.C. (1988). Tobacco smoking: A comparison between alcohol and drug abuse in patients. *Addictive Behaviors* 13(2), 185-190.
- Carmelli, D., Swan, G.E., & Robinette, D. (1993). The relationship between quitting smoking and changes in drinking in World War II veteran twins. *Journal of Substance Abuse Treatment* 5, 103-116.
- Centers for Disease Control and Prevention. (1999). Achievements in public health, 1900-1999: Tobacco use—United States, 1900-1999. *Morbidity and Mortality Weekly Report* 48(43), 986-993.
- Chengappa, K.N.R., Kambhampati, R.K., Perkins, K.A., Nigam, R., Anderson, T., Brar, J.S., Vermulapalli, H.K., Alzert, R., Key, P., & Levine, J. (in press). Bupropion SR as a smoking cessation treatment in remitted depressed patients maintained on selective serotonin reuptake inhibitor antidepressants. *Journal of Clinical Psychiatry*.
- Choi, W.S., Patten, C.A., Gillin, J.C., Kaplan, R.M., & Pierce, J.P. (1997). Cigarette smoking predicts development of depressive symptoms among U.S. adolescents. *Annals of Behavioral Medicine* 19, 42-50.
- Clarke, P.B. (1993). Nicotine dependence—mechanisms and therapeutic strategies. *Biochemical Society Symposia* 59, 83-95.
- Colby, S.M., Monti, P.M., Rohsenow, D.J., Sirota, A.D., Abrams, D.B., & Niaura, R.S. (1994). Alcoholics' beliefs about quitting smoking during alcohol treatment: Do they make a difference? Paper presented at the *Annual Meeting of the Research Society on Alcoholism*, Maui, Hawaii.
- Cornelius, J.R., Salloum, I.M., Ehler, J.G., Jarrett, P.J., Cornelius, M.D., Black, A., Perel, J.M., & Thase, M.E. (1997). Double-blind fluoxetine in depressed alcoholic smokers. *Psychopharmacology Bulletin* 33, 165-170.
- Covey, L.S., Glassman, A.H., & Stetner, F. (1990). Depression and depressive symptoms in smoking cessation. *Comprehensive Psychiatry* 31, 350-354.
- Covey, L.S., Glassman, A.H., & Stetner, F. (1999). Naltrexone effects on short-term and long-term smoking cessation. *Journal of Addictive Diseases* 18(1), 31-40.
- Covey, L.S., Glassman, A.H., Stetner, F., & Becker, J.B. (1993). Effect of history of alcoholism or major depression on smoking cessation. *American Journal of Psychiatry* 150 (10), 1546-1547.
- Covey, L.S., Hughes, D.C., Glassman, A.H., Blazer, D.G., & George, L.K. (1994). Ever-smoking, quitting, and psychiatric disorders: Evidence from the Durham, North Carolina, Epidemiologic Catchment Area. *Tobacco Control* 3, 222-227.
- Cox, L.S., Patten, C.A., Niaura, R.S., Wolter, T.D., Hays, J.T., Rigotti, N., Sachs, D.P.L., Buist, A.S., Hurt, R.D., Croghan, I.T., & Offord, K.P. (in press). Efficacy of bupropion for relapse prevention in smokers with a past history of major depression or alcoholism. *Journal of Clinical Psychiatry*.
- Craig, T.J., & Vannatta, P.A. (1977). The association of smoking and drinking habits in a community sample. *Journal of Studies on Alcohol* 38, 1434-1439.
- Dale, L.C., Hurt, R.D., Offord, K.P., Lawson, G.M., Croghan, I.T., & Schroeder, D.R. (1995). High-dose nicotine patch therapy: Percentage of replacement and smoking cessation. *Journal of the American Medical Association* 274(17), 1353-1358.
- De Soto, C.B., O'Donnell, W.E., & De Soto, J.L. (1989). Long-term recovery in alcoholics. *Alcoholism, Clinical and Experimental Research* 13(5), 693-697.
- DiChiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America* 85(14), 5274-5278.

- DiFranza, J.R., & Guerrera, M.P. (1989). Hardcore smokers (letter). *Journal of the American Medical Association* 261(18), 2634–2635.
- DiFranza, J.R., & Guerrera, M.P. (1990). Alcoholism and smoking. *Journal of Studies on Alcohol* 51, 130–135.
- Ellingstad, T.P., Sobell, L.C., Sobell, M.B., Cleland, P.A., & Agrawal, S. (1999). Alcohol abusers who want to quit smoking: Implications for clinical treatment. *Drug & Alcohol Dependence* 54, 259–265.
- Engelmann, J. (1989). *Twelve Steps for Tobacco Users. For Recovering People Addicted to Nicotine*. Center City, MN: Hazelden Foundation.
- Fagerström, K.O., Schneider, N.G., & Lunell, E. (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology* 111, 271–277.
- Fiore, M.C., Bailey, W.C., Cohen, S.J., Dorfman, S.F., Goldstein, M.G., Gritz, E.R., Heyman, R.B., Jaen, C.R., Kottke, T.E., Lando, H.A., Mecklenburg, R.E., Mullen, P.D., Nett, L.M., Robinson, L., Stitzer, M.L., Tommasello, A.C., Villejo, L., & Pewers, M.E. (2000). *Treating Tobacco Use and Dependence. Clinical Practice Guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service.
- Fiore, M.C., Smith, S.S., Jorenby, D.E., & Baker, T.B. (1994). The effectiveness of the nicotine patch for smoking cessation: A meta-analysis. *Journal of the American Medical Association* 271(24), 1940–1947.
- Fredrickson, P.A., Hurt, R.D., Lee, G.M., Wingender, L., Croghan, I.T., Lauger, G., Gomez-Dahl, L., & Offord, K.P. (1995). High dose transdermal nicotine therapy for heavy smokers: Safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology* 122, 215–222.
- Fryer, J.D., & Lukas, R.J. (1999). Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine and ibogaine. *Journal of Pharmacology and Experimental Therapeutics* 288(1), 88–92.
- Gariti, P., Alterman, A.I., Barber, W., Bedi, N., Luck, G., & Cnaan, A. (1999). Cotinine replacement levels for a 21 mg/day transdermal nicotine patch in an outpatient treatment setting. *Drug & Alcohol Dependence* 54(2), 111–116.
- Glassman, A.H., Helzer, J.E., Covey, L.S., Cottler, L.B., Stetner, F., Tipp, J.E., & Johnson, J. (1990). Smoking, smoking cessation, and major depression. *Journal of the American Medical Association* 264, 1546–1549.
- Glassman, A.H., Stetner, F., Walsh, B.T., Raizman, P.S., Fleiss, J.L., Cooper, T.B., & Covey, L.S. (1988). Heavy smokers, smoking cessation, and clonidine: Results of a double-blind, randomized trial. *Journal of the American Medical Association* 259, 2863–2866.
- Glover, E.D., Sachs, D.P.L., Stitzer, M.L., Rennard, S.I., Wadland, W.C., Pomerleau, O.F., Nowak, R.T., Daughton, D.M., Glover, P.N., Hughes, J.R., & Gross, J. (1996). Smoking cessation in highly dependent smokers with 4 mg nicotine polacrilex. *American Journal of Health Behavior* 20(5), 319–332.
- Gritz, E.R. (1994). Reaching toward and beyond the year 2000 goals for cigarette smoking. *Cancer* 74, 1423–1432.
- Gulliver, S.B., Kalman, D., Rohsenow, D.J., Colby, S.M., Eaton, C.A., & Monti, P.M. (2000). Smoking and drinking among alcoholics in treatment: Cross-sectional and longitudinal relationships. *Journal of Studies on Alcohol* 61, 157–163.
- Hajek, P., West, R., Foulds, J., Nilsson, F., Burrows, S., & Meadow, A. (1999). Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine* 159, 2033–2038.
- Hall, S.M., Reus, V., Munoz, R., Sees, K.L., Humfleet, G., Hartz, D.T., Frederick, S., & Triffleman, E. (1998). Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Archives of General Psychiatry* 55, 683–690.
- Hanna, E.Z., & Grant, B.F. (1999). Parallels to early onset alcohol use in the relationship of early onset smoking with drug use and DSM-IV drug and depressive disorders: Findings from the National Longitudinal Epidemiologic Survey. *Alcoholism, Clinical and Experimental Research* 23, 513–522.

- Hayford, K.E., Patten, C.A., Rummans, T.A., Schroeder, D.R., Offord, K.P., Croghan, I.T., Glover, E.D., Sachs, D.P.L., & Hurt, R.D. (1999). Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *British Journal of Psychiatry* 174, 173–178.
- Hays, J.T., Hurt, R.D., Rigotti, N.A., Niaura, R., Gonzales, D., Durcan, M.J., Sachs, D.P., Wolter, T.D., Buist, A.S., Johnston, J.A., & White, J.D. (2001). Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. *Annals of Internal Medicine* 135, 423–433.
- Hays, J.T., Offord, K.P., Croghan, I.T., Patten, C.A., Schroeder, D.R., Hurt, R.D., Jorenby, D.E., & Fiore, M.C. (1999). Smoking cessation rates in active and recovering alcoholics treated for nicotine dependence. *Annals of Behavioral Medicine* 21, 1–8.
- Hays, J.T., Wolter, T.D., Eberman, K.M., Croghan, I.T., Offord, K.P., & Hurt, R.D. (2001). Residential (inpatient) treatment compared with outpatient treatment for nicotine dependence. *Mayo Clinic Proceedings* 76, 124–133.
- Hughes, J.R. (1993). Treatment of smoking cessation in smokers with past alcohol/drug problems. *Journal of Substance Abuse Treatment* 10, 181–187.
- Hughes, J.R. (1995). Treatment of nicotine dependence. Is more better? (editorial). *Journal of the American Medical Association* 274(17), 1390–1391.
- Hughes, J.R. (1996). Clinical implications of the association between smoking and alcoholism. In J.B. Fertig & J.P. Allen (eds.), *Alcohol and Tobacco: From Basic Science to Clinical Practice*, NIAAA Research Monograph 30. Washington, D.C.: U.S. Government Printing Office, pp. 171–185.
- Hughes, J.R., Lesmes, G.R., Hatsukami, D.K., Richmond, R.L., Lichtenstein, E., Jorenby, D.E., Broughton, J.O., Fortmann, S.P., Leischow, S.J., McKenna, J.P., Rennard, S.I., Wadland, W.C., & Heatley, S.A. (1999). Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine and Tobacco Research* 1, 169–174.
- Hughes, J.R., Rose, G.L., & Callas, P.W. (2000). Nicotine is more reinforcing in smokers with past alcoholism than in smokers without this history. *Alcoholism, Clinical and Experimental Research* 24, 1633–1638.
- Hurt, R.D., Ahlskog, E., Croghan, G.A., Offord, K.P., Wolter, T.D., Croghan, I.T., & Moyer, T.P. (2000). Carbidopa/levodopa for smoking cessation: A pilot study with negative results. *Nicotine and Tobacco Research* 2, 71–78.
- Hurt, R.D., Croghan, I.T., Offord, K.P., Eberman, K.M., & Morse, R.M. (1995). Attitudes toward nicotine dependence among chemical dependency unit staff: Before and after a smoking cessation trial. *Journal of Substance Abuse Treatment* 12(4), 247–252.
- Hurt, R.D., Dale, L.C., Fredrickson, P.A., Caldwell, C.C., Lee, G.M., Offord, K.P., Lauger, G.G., Marusic, Z., Neese, L.W., & Lundberg, T.G. (1994). Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up—one-year outcome and percentage nicotine replacement. *Journal of the American Medical Association* 271(8), 595–600.
- Hurt, R.D., Dale, L.C., Offord, K.P., Bruce, B.K., McClain, F.L., & Eberman, K.M. (1992). Inpatient treatment of severe nicotine dependence. *Mayo Clinic Proceedings* 67, 823–828.
- Hurt, R.D., Dale, L.C., Offord, K.P., Croghan, I.T., Hays, J.T., & Gomez-Dahl, L. (1995). Nicotine patch therapy for smoking cessation in recovering alcoholics. *Addiction* 90, 1541–1546.
- Hurt, R.D., Dale, L.C., Offord, K.P., Lauger, G.G., Baskin, L.B., Lawson, G.M., Jiang, N.S., & Hauri, P.J. (1993). Serum nicotine and cotinine levels during nicotine patch therapy. *Clinical Pharmacology and Therapeutics* 54(1), 98–106.
- Hurt, R.D., Eberman, K.M., Croghan, I.T., Offord, K.P., Davis, L.J., Morse, R.M., Palmen, M.A., & Bruce, B.K. (1994). Nicotine dependence treatment during inpatient treatment for other addictions: A prospective intervention trial. *Alcoholism Clinical and Experimental Research* 18(4), 867–872.
- Hurt, R.D., Eberman, K.M., Slade, J., & Karan, I. (1993). Treating nicotine dependence in patients with other addictive disorders. In C. T. Orleans & J. Slade (eds.), *Nicotine Addiction: Principles and Management*. New York: Oxford University Press, pp. 310–326.
- Hurt, R.D., Finlayson, R.E., Morse, R.M., & Davis, L.J. (1988). Alcoholism in elderly persons: Medical aspects and prognosis in 216 inpatients. *Mayo Clinic Proceedings* 63, 753–760.

- Hurt, R.D., Offord, K.P., Croghan, G.A., Croghan, I.T., Gomez-Dahl, L., Wolter, T.D., Dale, L.C., & Moyer, T.P. (1998). Temporal effects of nicotine nasal spray and gum on nicotine withdrawal symptoms. *Psychopharmacology* 140, 98–104.
- Hurt, R.D., Offord, K.P., Croghan, I.T., Gomez-Dahl, L., Kottke, T.E., Morse, R.M., & Melton, L.J.I. (1996). Mortality following inpatient addictions treatment: Role of tobacco use in a community-based cohort. *Journal of the American Medical Association* 275(14), 1097–1103.
- Hurt, R.D., Sachs, D.P.L., Glover, E.D., Offord, K.P., Johnston, J.A., Dale, L.C., Khayrallah, M.A., Schroeder, D.R., Glover, P.N., Sullivan, C.R., Croghan, I.T., & Sullivan, P.M. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine* 337, 1195–1202.
- Hutchison, K.E., Monti, P.M., Rohsenow, D.J., Swift, R.M., Colby, S.M., Gnys, M., Niaura, R.S., & Sirota, A.D. (1999). Effects of naltrexone with nicotine replacement on smoking cue reactivity: Preliminary results. *Psychopharmacology* 142, 139–143.
- Johnston, J.A., Lineberry, C.G., Ascher, J.A., Davidson, J., Khayrallah, M.A., Feighner, J.P., & Stark, P. (1991). A 102-center prospective study of seizure in association with bupropion. *Journal of Clinical Psychiatry* 52(11), 450–456.
- Jorenby, D.E., Leischow, S.J., Nides, M., Rennard, S.I., Johnston, J.A., Hughes, A.R., Smith, S.S., Muramoto, M.L., Daughton, D.M., Doan, K., Fiore, M.C., & Baker, T.B. (1999). A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine* 340(9), 685–691.
- Jorenby, D.E., Smith, S.S., Fiore, M.C., Hurt, R.D., Offord, K.P., Croghan, I.T., Hays, J.T., Lewis, S.F., & Baker, T.B. (1995). Varying nicotine patch dose and type of smoking cessation counseling. *Journal of the American Medical Association* 274(17), 1347–1352.
- Joseph, A.M., Nichol, K.L., Willenbring, M.L., Korn, J.E., & Lysaght, L.S. (1990). Beneficial effects of treatment of nicotine dependence during an inpatient substance abuse treatment program. *Journal of the American Medical Association* 263, 3043–3046.
- Joseph, A.M., Willenbring, M.L., Nugent, S.M., & Nelson, D. (in press). Timing of Alcohol and Smoking Cessation (TASC): Study design, screening results and baseline characteristics.
- Kalman, D., Hayes, K., Colby, S.M., Eaton, C.A., Rohsenow, D.J., & Monti, P.M. (2001). Concurrent versus delayed smoking cessation treatment for persons in early alcohol recovery: A pilot study. *Journal of Substance Abuse Treatment* 20, 233–238.
- Kandel, D., Chen, K., Warner, L.A., Kessler, R.C., & Grant, B. (1997). Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. *Drug and Alcohol Dependence* 44, 11–29.
- Keenan, R.M., Hatsukami, D.K., Pickens, R.W., Gust, S.W., & Strelow, L.J. (1990). The relationship between chronic ethanol exposure and cigarette smoking in the laboratory and the natural environment. *Psychopharmacology* 100, 77–83.
- Kendler, K.S., Neale, M.C., MacLean, C.J., Heath, C.W., Jr., Eaves, L.J., & Kessler, R.C. (1993). Smoking and major depression: A casual analysis. *Archives of General Psychiatry* 50, 36–43.
- Kenford, S.L., Fiore, M.C., Jorenby, D.E., Smith, S.S., Wetter, D., & Baker, T.B. (1994). Predicting smoking cessation. Who will quit with and without the nicotine patch. *Journal of the American Medical Association* 271(8), 589–594.
- Kessler, R.C., Nelson, C.B., McGonagle, K.A., Edlund, M.J., Frank, R.G., & Leaf, P.J. (1996). The epidemiology of co-occurring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry* 66(1), 17–31.
- Kornitzer, M., Boutsen, M., Dramaix, M., Thijss, J., & Gustavsson, G. (1995). Combined use of nicotine patch and gum in smoking cessation: A placebo-controlled clinical trial. *Preventive Medicine* 24(1), 41–47.
- Kozlowski, L.T., Henningfield, J.E., Keenan, R.M., Lei, H., Leigh, G., Jelinek, L.C., Pope, M.A., & Haertzen, C.A. (1993). Patterns of alcohol, cigarette, and caffeine and other drug use in two drug abusing populations. *Journal of Substance Abuse Treatment* 10, 171–179.
- Kozlowski, L.T., Jelinek, L.C., & Pope, M.A. (1986). Cigarette smoking among alcohol abusers: A continuing and neglected problem. *Canadian Journal of Public Health* 77, 205–207.

- Kozlowski, L.T., Skinner, W., Kent, C., & Pope, M.A. (1989). Prospects for smoking treatment in individuals seeking treatment for alcohol and other drug problems. *Addictive Behaviors* 14, 273-278.
- Kozlowski, L.T., Wilkinson, A., Skinner, W., Kent, C., & Franklin, T. (1989). Comparing tobacco cigarette dependence with other drug dependencies: Greater or equal "difficulty quitting" and "urges to use," but less "pleasure" from cigarettes. *Journal of the American Medical Association* 261, 898-901.
- Lawson, G.M., Hurt, R.D., Dale, L.C., Offord, K.P., Croghan, I.T., Schroeder, D.R., & Jiang, N.S. (1998a). Application of serum nicotine and plasma cotinine concentrations to assess nicotine replacement in light, moderate, and heavy smokers undergoing transdermal therapy. *Journal of Clinical Pharmacology* 38(6), 502-509.
- Lawson, G.M., Hurt, R.D., Dale, L.C., Offord, K.P., Croghan, I.T., Schroeder, D.R., & Jiang, N.S. (1998b). Application of urine nicotine and cotinine excretion rates to assess nicotine replacement in light, moderate and heavy smokers undergoing transdermal therapy. *Journal of Clinical Pharmacology* 38(6), 510-516.
- Leischow, S.J., Nilsson, F., Franzon, M., Hill, A., Otte, P., & Merikle, E.P. (1996). Efficacy of the nicotine inhaler as an adjunct to smoking cessation. *American Journal of Health and Behavior* 20(5), 364-371.
- Lunell, E., Bergström, M., Antoni, G., Långström, B., & Nordberg, A. (1996). Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography (letter to editor). *Clinical Pharmacology and Therapeutics* 59(5), 593-594.
- Lunell, E., Molander, L., Ekberg, K., & Wahren, J. (2000). Site of nicotine absorption from a vapour inhaler—comparison with cigarette smoking. *European Journal of Clinical Pharmacology* 55(10), 737-741.
- Maletzky, B.M., & Klotter, J. (1974). Smoking and alcoholism. *American Psychologist* 131, 445-447.
- Marks, J.L., Hill, E.M., Pomerleau, C.S., Mudd, S.A., & Blow, E.C. (1997). Nicotine dependence and withdrawal in alcoholic and nonalcoholic ever-smokers. *Journal of Substance Abuse Treatment* 14, 521-527.
- Martin, J.E., Calfas, K.J., Patten, C.A., Polarek, M., Hofstetter, C.R., Noto, J., & Beach, D. (1997). Prospective evaluation of three smoking interventions in 205 recovering alcoholics: One-year results of Project SCRAP-Tobacco. *Journal of Consulting and Clinical Psychology* 65(1), 190-194.
- McGinnis, J.M., & Foege, W.H. (1993). Actual causes of death in the United States. *Journal of the American Medical Association* 270, 2207-2212.
- McIlvain, H.E., Bobo, J.K., Leed-Kelly, A., & Sitorius, M.A. (1998). Practical steps to smoking cessation for recovering alcoholics. *American Family Physician* 57, 1869-1876+.
- Miller, W.R., & Cervantes, E.A. (1997). Gender and patterns of alcohol problems: Pretreatment responses of women and men to the comprehensive drinker profile. *Journal of Clinical Psychology* 53, 263-277.
- Miller, W.R., Hedrick, K.E., & Taylor, C.A. (1983). Addictive behaviors and life problems before and after behavioral treatment of problem drinkers. *Addictive Behaviors* 8, 403-412.
- Mirand, A.L., & Welte, J.W. (1996). Alcohol consumption among the elderly in a general population, Erie County, New York. *American Journal of Public Health* 86, 978-984.
- Myers, M., & Brown, S. (1994). Smoking and health in substance abusing adolescents: A two-year follow-up. *Pediatrics* 93, 561-566.
- Myers, M.G., & Brown, S.A. (1997). Cigarette smoking four years following treatment for adolescent substance abuse. *Journal of Child and Adolescent Substance Abuse* 7, 1-15.
- Myers, M.G., Brown, S.A., & Kelly, J.F. (2000). A smoking intervention for substance abusing adolescents: Outcomes, predictors of cessation attempts, and post-treatment substance use. *Journal of Child and Adolescent Substance Abuse* 9, 77-91.
- Myers, M.G., Brown, S.A., & Kelly, J.F. (in press). A cigarette smoking intervention for substance abusing adolescents. Cognitive and behavioral practice.
- Myers, M.G., Kelly, J.E., & Lennox, G.A. (1997). Nicotine dependence and motivation for smoking cessation among substance abusing adolescents. Paper presented at the *Society of Behavioral Medicine Annual Meeting*, San Francisco, CA, April 1997.

- Novy, P.L., Hughes, J.R., Jensen, J.A., Hatsukami, D.K., & Huston, J. (1999). The efficacy of the nicotine patch in recovering alcoholic smokers. In L. Harris (ed.), *Problems of Drug Dependence 1998, NIDA Research Monograph 179* (Vol. 91). Washington, DC: USDHHS.
- Orleans, C.T., & Hutchinson, D. (1993). Tailoring nicotine addiction treatments for chemical dependency patients. *Journal of Substance Abuse Treatment 10*, 197–208.
- Paoletti, P., Fornai, E., Maggiorelli, F., Puntoni, R., Viegi, G., Carrozzini, L., Corlando, A., Gustavsson, G., Säwe, U., & Giuntini, C. (1996). Importance of baseline cotinine plasma values in smoking cessation: Results from a double-blind study with nicotine patch. *European Respiratory Journal 9*, 643–651.
- Patten, C.A., Drews, A., Myers, M.G., Martin, J.E., & Wolter, T.D. (in press). Effect of depressive symptoms on smoking abstinence among alcohol dependent smokers. *Psychology of Addictive Behaviors*.
- Patten, C.A., Martin, J.E., Calfas, K.J., Lento, J., & Wolter, T.D. (2001). Behavioral treatment for smokers with a history of alcoholism: Predictors of successful outcome. *Journal of Consulting and Clinical Psychology 69*(5), 796–801.
- Patten, C.A., Martin, J.E., Hofstetter, C.R., Brown, S.A., Kim, N., & Williams, C. (1999). Smoking cessation following treatment in a smoke-free Navy alcohol rehabilitation program. *Journal of Substance Abuse Treatment 16*, 61–69.
- Patten, C.A., Martin, J.E., Myers, M.G., Calfas, K.J., & Williams, C.D. (1998). Effectiveness of cognitive-behavioral therapy for smokers with histories of alcohol dependence and depression. *Journal of Studies on Alcohol 59*, 327–335.
- Patten, C.A., Martin, J.E., & Owen, N. (1996). Can psychiatric and chemical dependency treatment units be smoke free? *Journal of Substance Abuse Treatment 13*, 107–118.
- Patten, C.A., Schneekloth, T.D., Morse, R.M., Herrick, L.M., Offord, K.P., Wolter, T.D., Williams, B.A., & Hurt, R.D. (2001). Effect of current tobacco use and history of an alcohol problem on health status in hospitalized patients. *Addictive Behaviors 26*, 129–136.
- Pontieri, F.E., Tanda, G., Orzi, F., & DiChiara, G. (1996). Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature 382*, 255–257.
- Prochazka, A.V., Weaver, M.J., Keller, R.T., Fryer, G.E., Licari, P.A., & Lofaso, D. (1998). A randomized trial of nortriptyline for smoking cessation. *Archives of Internal Medicine 158*, 2035–2039.
- Ravenholt, R.T. (1984). Addiction mortality in the United States. *Population and Development Review 4*, 697–725.
- Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., & Goodwin, K.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. *Journal of the American Medical Association 264*, 2511–2518.
- Robertson, N. (1988). *Getting Better: Inside Alcoholics Anonymous*. New York: William Morrow.
- Rohsenow, D.J., Monti, P.M., Colby, S.M., Gulliver, S.B., Sirota, A.D., Niaura, R.S., & Abrams, D.B. (1997). Effects of alcohol cues on smoking urges and topography among alcoholic men. *Alcoholism, Clinical and Experimental Research 21*, 101–107.
- Rose, J.E., Behm, F.M., Westman, E.C., Levin, E.D., Stein, R.M., & Ripka, G.V. (1994). Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clinical Pharmacology and Therapeutics 56*(1), 86–99.
- Rose, J.E., Westman, E.C., & Behm, F.M. (1996). Nicotine/mecamylamine combination treatment for smoking cessation. *Drug Development Research 38*, 243–256.
- Russell, M.A.H., Raw, M., & Jarvis, M.J. (1980). Clinical use of nicotine chewing gum. *British Medical Journal 280*, 1599–1602.
- Rustin, T.A. (1998). Incorporating nicotine dependence into addiction treatment. *Journal of Addictive Diseases 17*, 83–108.
- Sachs, D.P.L. (1995). Effectiveness of the 4-mg dose of nicotine polacrilex for the initial treatment of high-dependent smokers. *Archives of Internal Medicine 155*, 1973–1980.
- Sachs, D.P.L., Benowitz, N.L., Bostrom, A.G., & Hansen, M.D. (1995). Percent serum replacement and success of nicotine patch therapy. *American Journal of Respiratory and Critical Care Medicine 151*, A688.

- Saxon, A.J., McGuffin, R., & Walker, R.D. (1997). An open trial of transdermal nicotine replacement therapy for smoking cessation among alcohol- and drug-dependent inpatients. *Journal of Substance Abuse Treatment* 14, 333–337.
- Schneider, N.G., Lunell, E., Olmstead, R.E., & Fagerström, K.O. (1996). Clinical pharmacokinetics of nasal nicotine delivery: A review and comparison to other nicotine systems. *Clinical Pharmacokinetics* 31(1), 65–80.
- Schneider, N.G., Olmstead, R., Mody, F.V., Doan, K., Franzon, M., Jarvik, M.E., & Steinberg, C. (1995). Efficacy of a nicotine nasal spray in smoking cessation: A placebo-controlled, double-blind trial. *Addiction* 90(12), 1671–1682.
- Schuckit, M.A. (1986). Genetic and clinical implications of alcoholism and affective disorder. *American Journal of Psychiatry* 143, 140–147.
- Schuh, K.J., Schuh, L.M., Henningfield, J.E., & Stitzer, M.L. (1997). Nicotine nasal spray and vapor inhaler: Abuse liability assessment. *Psychopharmacology* 130(4), 352–361.
- Seider, A.L., Burling, T.A., Gaither, D.E., & Thomas, R.G. (1996). Substance-dependent inpatients who accept smoking treatment. *Journal of Substance Abuse* 8, 33–44.
- Sellers, E.M., Naranjo, C., & Kadlec, K. (1987). Do serotonin uptake inhibitors decrease smoking? Observations in a group of heavy drinkers. *Journal of Clinical Psychopharmacology* 7(6), 417–420.
- Slemmer, J.E., Martin, B.R., & Damaj, M.I. (in press). Bupropion is a nicotinic antagonist. *Journal of Pharmacology and Experimental Therapeutics*.
- Sobell, L.C., Sobell, M.B., & Toneatto, T. (1991). Recovery from alcohol problems without treatment. In N. Heather, W.R. Miller & J. Greeley (eds.), *Self-Control and Addictive Behaviors*. New York: Pergamon Press, pp. 198–242.
- Sobell, M.B., & Sobell, L.C. (1993). The longitudinal study of dual recoveries from smoking and alcohol problems. Paper presented at the *Association for Advancement of Behavioral Therapy Annual Meeting*.
- Sobell, M.B., Sobell, L.C., & Kozlowski, L.T. (1995). Dual recovery from alcohol and smoking problems. In J.B. Fertig & J.P. Allen (eds.), *Alcohol and Tobacco: From Basic Science to Clinical Practice*. Washington, D.C.: US DHHS, pp. 207–224.
- Stapleton, J.A., Russell, M.A., Feyerabend, C., Wiseman, S.M., Gustavsson, G., Sawe, U., & Wiseman, D. (1995). Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction* 90, 31–42.
- Sussman, S. (in press). Smoking cessation among persons in recovery. *Substance Use and Misuse*.
- Sutherland, G., Stapleton, J.A., Russell, M.A.H., Jarvis, M.J., Hajek, P., Belcher, M., & Feyerabend, C. (1992). Randomized controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 340, 324–329.
- Toneatto, A., Sobell, L.C., Sobell, M.B., & Kozlowski, L.T. (1995). Effect of cigarette smoking on alcohol treatment outcome. *Journal of Substance Abuse* 7, 245–252.
- Tonnesen, P., Paoletti, P., Gustavsson, G., Russell, M.A., Saracci, R., Gulsvik, A., Rijcken, B., & Sawe, U. (1999). Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE trial. *European Respiratory Journal* 13, 238–246.
- Vaillant, G.E., Schnurr, P.P., Baron, J.A., & Gerber, P.D. (1991). A prospective study of the effects of cigarette smoking and alcohol abuse on mortality. *Journal of General Internal Medicine* 6, 299–304.
- Wong, G.Y., Wolter, T.D., Croghan, G.A., Croghan, I.T., Offord, K.P., & Hurt, R.D. (1999). A randomized trial of naltrexone for smoking cessation. *Addiction* 94(8), 1227–1237.
- Zevin, S., Jacob, P., & Benowitz, N.L. (1998). Dose-related cardiovascular and endocrine effects of transdermal nicotine. *Clinical Pharmacology and Therapeutics* 64, 87–95.
- Zimmerman, R.S., Warheit, G.J., Ulrich, P.M., & Auth, J.B. (1990). The relationship between alcohol use and attempts and success at smoking cessation. *Addictive Behaviors* 15, 197–207.

Alcohol and Psychiatric Comorbidity

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Abstract. Comorbid psychiatric disorders and drug use disorders (DUDs) are common among alcoholics (Regier, Farmer, Rae, Locke, Keith, Judd, & Goodwin, 1990; Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen, & Kendler, 1994). These comorbid disorders often predict a shorter time to relapse of alcoholism (Greenfield, Weiss, Muenz, Vagge, Kelly, Bello, & Michael, 1998). However, despite the prevalence and the adverse effects of this comorbidity, few controlled treatment studies have been conducted involving this dual diagnosis population (Litten & Allen, 1999). To date, most of these few studies of alcoholics with comorbid disorders have been restricted to studies of alcoholics with either comorbid major depression or comorbid anxiety disorders (Litten & Allen, 1995). The results of these trials suggest efficacy for SSRI antidepressants and tricyclic antidepressants for treating alcoholics with comorbid major depression and suggest efficacy for buspirone for treating alcoholics with comorbid anxiety disorders (Mason, Kocsis, Ritvo, & Cutler, 1996; Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase, & Black, 1997; Kranzler, Burleson, Del Boca, Babor, Korner, Brown, & Bohn, 1994). However, controlled treatment studies involving alcoholics with other comorbid disorders are almost totally lacking. Consequently, to date, no empirically proven treatment exists for most of these comorbid disorders.

Medications development is a rapidly growing priority for the National Institute on Alcohol Abuse and Alcoholism (Litten & Allen, 1998). During the 5-year period from 1991 to 1996, the NIAAA extended funding of human pharmacological studies from 8 projects to 25 projects (Litten & Fertig, 1996). However, few of the treatment studies funded by NIAAA have involved alcoholics with comorbid disorders. For example, in 1998, NIAAA was funding 28 pharmacotherapy studies involving alcoholics, but only 3 of these 28 studies focused on alcoholism with comorbid depression (Litten & Allen, 1998). Consequently, to date, a number of large gaps in knowledge continue to exist involving the treatment of alcoholics with comorbid disorders. For example,

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almost no double-blind, placebo-controlled studies have been completed involving alcoholics with many various comorbid conditions, such as dysthymic disorder, posttraumatic stress disorder, bipolar I or bipolar II disorder, schizophrenia, attention deficit hyperactivity disorder, DUDs, suicidality, or a variety of "trimorbid" conditions. Controlled studies involving special populations with comorbid disorders are also almost entirely lacking, such as controlled studies involving adolescent or geriatric patients (Vitiello & Jensen, 1997; Cornelius, Bukstein, Birmaher, Salloum, Lynch, Pollock, Gershon, & Clark, 2001). Little work has been done to clarify the optimal dose, duration of treatment, and sequence of treatment for various comorbid conditions (Litten & Allen, 1999). Longer term studies, combination medication studies, and studies evaluating the optimal combination of pharmacotherapy and psychotherapy are scarce (Project MATCH Research Group, 1998; Cornelius, Salloum, Haskett, Daley, Cornelius, Thase, & Perel, 2000; Salloum, Cornelius, Thase, Daley, Kirisci, & Spotts, 1998; O'Malley & Carroll, 1996). In addition, little work has been done to evaluate predictors of treatment response, subtypes of dual disorders, and matching of dual disorder subjects to optimal treatment (Nunes, McGrath, Quitkin, Stewart, Goehl, & Ocepek-Welikson, 1996; Litten & Allen, 1998). Effectiveness trials (as opposed to efficacy trials) are scarce, as are studies conducted in conjunction with basic sciences studies to clarify the biological mechanisms underlying both disorders and underlying treatment response (Brady, Halligan, & Malcolm, 1999). Also, few studies have been conducted to clarify how treatment of either the alcoholism or the psychiatric disorder of dual disorder patients affects the outcome of the other disorder (Litten & Allen, 1999). Research is clearly warranted in these areas involving the treatment of alcoholics with comorbid disorders.

1. Introduction

The comorbidity of alcohol use disorders (AUDs) with psychiatric disorders and with other DUDs is now recognized as a common clinical problem. Two recent large epidemiological surveys emphasized the prevalence of comorbid psychiatric and DUDs among alcoholics in community samples, the Epidemiologic Catchment Area (ECA) Study (Regier et al., 1990) and the National Comorbidity Survey (NCS) (Kessler et al., 1994). The ECA study reported that 45% of individuals with an AUD had at least one co-occurring psychiatric or other drug disorder (Regier et al., 1990) and also reported a significant association between the AUDs and the comorbid disorders (Helzer & Pryzbeck, 1998). The NCS study reported that the vast majority of lifetime disorders in their sample (79%) were comorbid disorders (Kessler et al., 1994) and that the comorbidity was more highly concentrated than previously recognized in roughly one-sixth of the population that had a history of three or more comorbid disorders. The NCS data have shown that lifetime comorbidity

among those with AUDs is associated with the persistence of alcohol abuse (Kessler, Crum, Warner, Nelson, Schulenberg, & Anthony, 1997), and McLellan, Luborsky, Woody, O'Brien, and Druley (1983) showed that AUD individuals with high psychiatric severity demonstrate virtually no improvements in any treatment. However, despite the prevalence and adverse consequences of comorbidity among individuals with AUDs, little research has been devoted to the study of pharmacological agents or other treatments that might treat these problems (Litten & Allen, 1995).

Medications development is a rapidly growing priority for the National Institute on Alcohol Abuse and Alcoholism (Litten & Allen, 1998). For example, during the 5-year period from 1991 to 1996, the NIAAA extended funding of human pharmacological studies from 8 projects to 25 projects (Litten & Fertig, 1996). However, few of the treatment studies funded by NIAAA or other NIH institutes have involved alcoholics with comorbid disorders (Litten & Allen, 1998). For example, in 1998, NIAAA was funding 28 pharmacotherapy studies involving alcoholics, but only 3 of these 28 studies involved alcoholism with comorbid depression (Litten & Allen, 1998). Consequently, large gaps in knowledge continue to exist involving the treatment of alcoholics with comorbid disorders.

The reasons for the lack of studies involving comorbid populations are unclear but may involve methodological, clinical, fiscal, feasibility, and political considerations. *Methodological considerations* are associated with the need for multiple outcome dimensions in comorbidity research. In contrast, a focus on a single problem, such as alcohol dependence, substantially simplifies design considerations in planning treatment research. *Clinical considerations* make comorbidity research more labor-intensive than studies involving single diagnosis populations because individuals with multiple conditions are typically more difficult to manage. For example, in patients with AUDs and depression, suicidal ideas are more common than for other AUD subgroups, and monitoring of suicidal ideas is necessary. Clinical considerations lead to the need for specially trained and experienced staff. *Fiscal considerations*, therefore, represent another potential difficulty in carrying out such research because more expense in research personnel and closer supervision are needed. *Feasibility considerations* may be introduced by the typical focus on specific comorbidity subgroups, making recruitment more problematic. *Political considerations* may also be raised by the fact that comorbidity research typically bestrides the primary topic areas of multiple NIH institutes.

This chapter will review alcohol and psychiatric comorbidity and treatment for these comorbid disorders. Because of space limitations, this chapter will address only the most common and clinically relevant comorbid conditions. This chapter will also focus on pharmacotherapy rather than psychotherapy of dual diagnosis populations because almost all of the controlled treatment studies to date of dual diagnosis populations have involved pharmacotherapy trials rather than psychotherapy trials.

2. Comorbidity with Major Depression

Because of their relatively high overall lifetime prevalence and frequent association with AUDs in the literature, affective disorders will be considered in greater detail in this manuscript than other comorbid disorders. The NCS study reported that the most common psychiatric disorders in their sample were major depression (17%) and alcohol dependence (14%) (Kessler et al., 1994). Helzer and Pryzbeck (1998) reported a significant association between AUD and depressive disorders. Perhaps reflecting this particularly prevalent comorbidity, more treatment studies have been conducted involving AUD with affective disorders than with any other class of comorbid disorder.

A few recent well-controlled studies have been conducted that evaluated the efficacy of tricyclic antidepressants in individuals with comorbid AUD and major depressive disorder. McGrath, Nunes, Stewart, Goldman, Agosti, Ocepek-Welikson, & Quitkin (1996) studied the tricyclic antidepressant imipramine versus placebo in 69 alcoholics with primary depression. They found that treatment with imipramine was associated with improvement in depression, but no overall effect on drinking outcome was observed. A study of nortriptyline by Powell, Campbell, Landon, Liskou, Thomas, Nickel, Dale, Penick, Samuelson, & Lacoursiere (1995) showed no significant improvement versus placebo for either the depressive symptoms or the drinking of their depressed alcoholics. Mason and colleagues (1996) conducted a study of 71 patients with primary alcohol dependence, 28 of whom had major depression secondary to alcoholism. They found that final HAM-D scores of desipramine patients significantly decreased relative to those of placebo patients; baseline HAM-D was the covariate. Survival curves demonstrated a significant difference between placebo and desipramine in time to relapse, favoring the desipramine group. These findings suggested that desipramine is efficacious in treating the depressive symptoms of alcoholics with secondary major depression and that a statistically significant increase in length of abstinence is noted among those with comorbid depression who are treated with desipramine. However, the use of desipramine to reduce relapse in nondepressed alcoholics was not supported. The authors of that article suggested that selective serotoninergic (SSRI) antidepressants might have certain advantages over tricyclic antidepressants, such as greater tolerability and lower toxicity in overdose.

To date, only a few double-blind, placebo-controlled studies have evaluated the efficacy of SSRI antidepressants in individuals with comorbid alcohol dependence and major depression. These studies follow from the work of Naranjo, Kadlec, Sanhueza, Woodley-Remus, and Sellers (1990) involving fluoxetine in nondepressed alcohol abusers. One such study (Cornelius et al., 1997) evaluated the SSRI, fluoxetine, in 51 severely depressed subjects with comorbid major depression and alcohol dependence. In that study, fluoxetine demonstrated efficacy versus placebo for decreasing both the drinking and the depressive symptoms of this population. However, the authors cautioned that it was unclear to what extent these results generalized to the treatment of less

severely depressed and less suicidal alcoholics with major depression or to alcoholics with other less serious depressive disorders. The beneficial effects associated with fluoxetine treatment persisted at a 1-year follow-up evaluation (Cornelius et al., 2000). Kranzler, Burleson, Korner, Del Boca, Bohn, Brown, & Liebowitz (1995) conducted a trial of fluoxetine to prevent relapse in 101 alcoholics, 14 of whom demonstrated a current major depression. The study demonstrated that fluoxetine is not of use for relapse prevention with mild to moderate alcohol dependence and no comorbid depression. The authors also concluded that the medication might reduce depressive symptoms in alcoholics with major depression. The authors recommended that subsequent studies with fluoxetine should focus on more severely alcohol-dependent subjects or those with comorbid depression.

One study to date has assessed the efficacy of the SSRI medication, sertraline, in depressed alcoholics (Roy, 1998). This study involved 36 subjects who remained in an intensive day program throughout the study. The results of this study demonstrated the efficacy of sertraline versus placebo in decreasing the depressive symptoms of depressed alcoholics. However, the effects of sertraline on drinking by this population could not be adequately assessed because their treatment setting precluded them from drinking.

3. Comorbidity with Bipolar Disorder

In both the ECA study and the NCS study, it has been shown that bipolar disorder has a particularly high rate of co-occurrence with AUD. In the ECA study, the odds of having a bipolar disorder were five times greater if one had an AUD than if one did not have an AUD (Regier et al., 1990). In the NCS study, the odds of having a diagnosis of alcohol dependence were 12 times greater among those with a bipolar disorder than among those without a bipolar disorder, which was the highest odds ratio noted for any Axis I disorder (Kessler et al., 1997). However, despite increased awareness in recent years of the common co-occurrence of bipolar disorder and AUDs, no completed double-blind studies have addressed the efficacy of lithium or any other medication in this dual diagnosis population.

Even though no double-blind trials to date have evaluated the efficacy of lithium carbonate in bipolar alcoholics, several trials involving lithium have been conducted involving alcoholics with unipolar depression and alcoholics without an affective disorder. Fawcett, Clark, Aagesen, Pinasi, Tilkin, Sellers, McGuire, and Gibbons (1987) conducted a double-blind, placebo-controlled trial of lithium in a study group that included both depressed and non-depressed alcoholics. That study found no effects of lithium on the abstinence rates of depressed or nondepressed alcoholics. Dorus, Ostrow, Anton, Cushman, Collins, Schaefer, Charles, Desai, Hayashida, Malkerneker, Willenbring, Fiscella, and Sather (1989) conducted a multisite, double-blind, placebo-controlled trial in a study sample that included both depressed and

nondepressed alcoholic veterans. That study found no efficacy for lithium for any outcome measure in either the depressed or nondepressed alcoholics. Thus, lithium does not demonstrate efficacy in treating alcoholics with unipolar depression or alcoholics with no affective disorder.

The anticonvulsant medications carbamazepine and valproate have recently demonstrated efficacy in the treatment of bipolar disorder among non-alcoholics, including demonstration of efficacy among subtypes of bipolar disorder that are less responsive to lithium carbonate, such as rapid cycling, mixed, or dysphoric mania. Both controlled and uncontrolled clinical trials report that valproate is effective in acute and prophylactic treatment of mania in subjects who could not tolerate or had a poor response to lithium (Bowden, Brugger, Suann, Calabrese, Janicak, Petty, Dilsaver, Davis, Rush, Smally, Garza-Trevino, Risch, Goodnick, & Morris, 1994). A recent multisite, placebo-controlled study reported that valproate was as effective as lithium and more effective than placebo in acute mania (Bowden et al., 1994). However, to date, no trials of carbamazepine or valproate have been conducted in patients with comorbid bipolar disorder and an AUD.

4. Comorbidity with Anxiety Disorders

According to the National Comorbidity survey (Kessler et al., 1994), one in every four Americans reports a history of at least one anxiety disorder, making anxiety disorders roughly equivalent in prevalence to DUDs. That study also reported that anxiety disorders, as a group, are considerably more likely to occur in the 12 months before the interview (17%) than either DUDs (11%) or affective disorders (11%). The prevalence of other NCS disorders was quite low. In that study, 61% of women and 36% of men with any lifetime anxiety disorder reported a lifetime diagnosis of alcohol dependence, and these disorders were significantly correlated with each other. However, despite the prevalence of these disorders, only one pharmacological agent, buspirone, has been evaluated in clinical studies with alcoholics suffering anxiety disorders.

Buspirone is a partial 5-HT-1A agonist. Studies involving buspirone in alcoholics are based on the hypothesis that alteration in central nervous system serotonin function can predispose individuals to relapse (George, Rawlings, Eckardt, Phillips, Shoaf, & Linnoila, 1999). This hypothesis, in turn, is based on the apparent link between low serotonin turnover rate and increased alcohol consumption (George et al., 1999). To date, four clinical studies involving buspirone have been conducted on alcoholics with comorbid anxiety disorder, and two other double-blind, placebo-controlled studies involving buspirone have been conducted on alcoholics with no comorbid anxiety disorder. In the first of these studies involving alcoholics with comorbid anxiety disorder, Bruno (1989) studied patients with mild-to-moderate alcohol abuse and mild-to-moderate anxiety in an 8-week trial. That research group found that patients in the buspirone group experienced a lower drop-out rate, less craving, and a reduction in

alcohol consumption, depression, anxiety, and global psychopathology. Tollefson, Montague-Clouse, & Tollefson (1992) studied anxious alcoholic outpatients who had already abstained from alcohol for 30 to 90 days. The buspirone group in that study exhibited greater reduction in anxiety, a greater global reduction in drinking, fewer number of days of desiring alcohol, and better retention in treatment than the placebo group. Malcolm, Anton, Randall, Johnston, Brady, & Thevos (1992) studied a group of anxious alcoholics who had been detoxified in a veterans hospital and who subsequently had been followed for 6 months as outpatients. That research group found no therapeutic efficacy for buspirone for decreasing anxiety or for prolonging the maintenance of abstinence. Kranzler and colleagues (1994) conducted a randomized 12-week, placebo-controlled study of buspirone in 61 anxious alcoholics who were able to stop drinking for 7 days as outpatients. They found that buspirone treatment was associated with a greater reduction in the level of anxiety, a slower return to heavy alcohol consumption, a greater retention in the trial, and lesser number of drinking days during a 6-month follow-up period. In summary, three of the four studies in this area demonstrated the efficacy of buspirone for treating anxious alcoholics, and one did not. These findings suggest that buspirone is probably of benefit in treating at least some anxious alcoholics.

The first controlled study of buspirone in nonanxious alcoholics was conducted by Malec, Malec, Gagne, & Dongier (1996). That research group failed to find a reduction in alcohol consumption among alcoholics who were followed for 12 weeks. Similarly, George and colleagues (1999) found that treatment with buspirone did not increase the days to relapse in their sample of nonanxious alcoholics. These findings suggest that buspirone is probably not of benefit in treating alcoholics who do not display comorbid anxiety.

Other classes of pharmacotherapeutic agents, such as tricyclic antidepressants, SSRI antidepressants, monoamine oxidase inhibitors, and benzodiazepines have been studied for treating anxiety disorders in patients without comorbid alcoholism. However, to date, none of these classes of medications has been studied in alcoholics with anxiety disorders (Litten & Allen, 1995). Consequently, the efficacy of these medications in alcoholics with comorbid anxiety disorders remains unclear.

5. Comorbidity with Psychotic Disorders

The ECA study (Regier et al., 1990) reported that schizophrenia has a prevalence rate of only 3.8% among those with AUDs but that this disorder is seen three times more often among alcoholics than among nonalcoholics. Conversely, the prevalence of any AUD among schizophrenics is 34%, suggesting that comorbid alcohol disorders are a common problem among schizophrenics. To date, no controlled pharmacotherapy trials have been conducted in patients with comorbid schizophrenia and an AUD, so the efficacy of various medications in this population remains unclear. However, it has been

reported that disulfiram should be used with caution in this dual diagnosis population, because it may increase central levels of dopamine by blocking dopamine β -hydroxylase and thereby exacerbate psychosis (Wilkins, 1997).

6. Comorbidity with Drug Use Disorders

The National Comorbidity Survey (Kessler et al., 1997) reported that DUDs are the group of disorders that is most likely to co-occur with AUD, as they are present in 30% of these individuals. The ECA study (Regier et al., 1990) also demonstrated that an individual with a history of an AUD is six times more likely to have another DUD than an individual with no history of an AUD. However, despite the prevalence of these disorders among alcoholics, only a handful of small studies has addressed the treatment of this dual diagnosis population.

One such recent study involved the open-label use of fluoxetine in eight adolescent subjects with major depression, conduct disorder, and an AUD, generally in combination with other DUDs (Riggs, Mikulich, Coffman, & Crowley, 1997). This study demonstrated within-group efficacy of fluoxetine in decreasing depression. Potential effects on drug or alcohol use could not be assessed in this study because it was conducted in a controlled environment. Nonetheless, the results of this study suggest that double-blind, placebo-controlled studies with fluoxetine are warranted in this population.

Few papers have been published dealing with the pharmacotherapy of patients with cocaine comorbidity among alcoholics. Batki, Manfredi, Jacob, and Jones (1993) conducted a fluoxetine study in a sample of 16 patients who displayed cocaine dependence and opioid dependence and who were participating in methadone maintenance. Most of the subjects in that study also had a lifetime history of major depression, heavy alcohol use, and HIV positive blood tests. Cocaine use and cocaine craving both significantly decreased during the course of the study, and depressive symptoms and anxiety symptoms both significantly improved as well. In another study involving fluoxetine, a secondary data analysis was conducted focusing on a trimorbid subsample of 17 patients who displayed cocaine abuse in addition to alcohol dependence and major depression (Cornelius, Salloum, Thase, Haskett, Daley, Jones-Barlock, Upsher, & Perel, 1998). The results from that "trimorbid" subsample were compared to those of a subsample of 34 subjects who displayed alcohol dependence and major depression but who did not display comorbid cocaine abuse. In those analyses, comorbidity with cocaine abuse acted as a significant predictor of poor response for the depressive symptoms and drinking by this population, regardless of treatment group assignment. No significant difference between the fluoxetine group and the placebo group was noted for cocaine use, alcohol use, or depressive symptoms, though the limited sample sizes made it difficult to adequately test these potential differences. Thus, the efficacy of fluoxetine for treating this trimorbid population remains unclear.

The National Comorbidity Survey confirmed that marijuana is the most commonly used illicit drug in the United States (Anthony, Warner, & Kessler, 1994). However, to date, no controlled studies have evaluated the efficacy of any pharmacotherapeutic agent among pure marijuana abusers or among patients with comorbid alcoholism and marijuana abuse. However, one recent paper presented data from a secondary data analysis involving the subsample of 22 subjects with cannabis abuse drawn from a larger study group of patients with comorbid alcohol dependence and major depression (Cornelius, Salloum, Haskett, Ehler, Jarrett, Thase, & Perel, 1999). The results of that study suggested efficacy for fluoxetine versus placebo in decreasing the marijuana use by that population. However, no studies to date have either confirmed or refuted those findings. Consequently, the efficacy of pharmacotherapeutic agents for decreasing marijuana use by depressed or nondepressed alcoholics remains unclear.

7. Conclusions

1. To date, few if any double-blind, placebo-controlled pharmacotherapy studies have been conducted for many large populations that are comorbid with alcoholism. However, open-label studies have suggested efficacy of various medications for several of these populations. Controlled studies with these populations which are comorbid with alcoholism are clearly warranted, such as studies involving subjects with the following:
 - a. Dysthymic disorder (King, Naylor, Hill, Shain, & Greden, 1993).
 - b. Posttraumatic stress disorder.
 - c. Bipolar I and bipolar II disorder (Brady, Sonne, Anton, & Ballenger, 1995; Salloum, Cornelius, Mezzich, Kirisci, Daley, Spotts, & Zuckoff, 2001).
 - d. Schizophrenia and other psychotic disorders (Brady et al., 1999).
 - e. Drug use disorders (Cornelius, Salloum, et al., 1998; Cornelius, Perkins, Salloum, Thase, & Moss, 1999).
 - f. Attention deficit hyperactivity disorder (Bukstein, Glancy, & Kaminer, 1989).
 - g. Suicidal alcoholics (Cornelius, Salloum, Cornelius, Perel, Thase, Ehler, & Mann, 1993; Cornelius, Salloum, Mezzich, Cornelius, Fabrega, Ehler, Ulrich, Thase, & Mann, 1995; Cornelius, Salloum, Day, Thase, & Mann, 1996; Cornelius, Thase, Salloum, Cornelius, Black, & Mann, 1998; Cornelius, Salloum, Lynch, Clark, & Mann, 2001).
 - h. Various trimorbid populations (Kessler et al., 1994).
 - i. Nondependent, alcohol abusing subjects, with comorbid conditions (Litten & Allen, 1999).
2. Treatment studies involving comorbid samples of adolescents and geriatric populations (Bukstein et al., 1989; Vitiello & Jensen, 1997;

Clark, Pollock, Bukstein, Mezzich, Bromberger, & Donovan, 1997; Clark, Parker, & Lynch, 1999; Martin, Kaczynski, Maisto, Bukstein, & Moss, 1995; Cornelius, Bukstein, et al., 2001). To date, no placebo-controlled trials have been conducted in these populations, despite the recent demonstration of the efficacy of fluoxetine versus placebo in treating the depressive symptoms of nonalcoholic adolescents with major depression (Emslie, Rush, Weinberg, Kowatch, Hughes, Carmody, & Rintelmann, 1997).

3. Studies to clarify the optimal dose, duration, and sequence of treatment (Litten & Allen, 1999).
4. Longer term treatment studies to assess the longer-term efficacy of various treatments. To date, few such studies have been conducted in comorbid populations of alcoholics (Cornelius et al., 2000), though some longer term studies have recently been conducted in alcoholics without comorbid disorders (Project MATCH Research Group, 1998).
5. Combination medication studies, such as studies involving the use of a psychotropic medication in combination with naltrexone or acamprosate (Volpicelli, Alterman, Hayashida, & O'Brien, 1992; Paille, Guelfi, Perkins, Royer, Steru, & Parot, 1995). To date, no controlled trials of combination medication therapy have been conducted that involved alcoholics with comorbid disorders. However, a recent open-label study suggested efficacy for the combination of fluoxetine and naltrexone for treating depressed alcoholics (Salloum, Cornelius et al., 1998).
6. Studies assessing the optimal combination of pharmacotherapy in combination with psychotherapy among the populations of alcoholics with various comorbid disorders. To date, few controlled studies of this combination therapy have been conducted (O'Malley & Carroll, 1996).
7. Studies to determine the predictors and interactive effects of treatment response, such as gender, ethnicity, age, and pregnancy status (Cornelius, Jarrett, Thase, Fabrega, Haas, Jones-Barlock, Mezzich, & Ulrich, 1995; Cornelius, Fabrega, Cornelius, Mezzich, Maher, Salloum, Thase, & Ulrich, 1996) and to determine subtypes of dual disorders that may have different responses to treatment (Nunes et al., 1996). Such studies would aid in matching individuals with dual disorders to the optimal treatment for each individual (Litten & Allen, 1998).
8. Effectiveness trials (as opposed to an exclusive focus on efficacy trials) to determine the clinical utility of various treatments in various "real world" settings, such as jails and state hospitals.
9. Studies that do not focus exclusively on the level of alcohol use and the level of psychopathology but also include other important outcome measures. For example, studies that focus on patient compliance, level of functioning, patient satisfaction, treatment utilization, medication side effects, problem awareness, treatment readiness, or the role of patients' expectations are warranted (Litten & Fertig, 1996; Cornelius,

- Pringle, Jernigan, Kirisci, & Clark, 2001). To date, very few studies involving these factors have been conducted in populations of alcoholics with comorbid conditions.
10. Treatment studies conducted in conjunction with basic sciences studies are warranted to clarify the biological mechanisms underlying both disorders and underlying treatment response (Brady et al., 1999).
 11. Studies to clarify how treatment of either the alcoholism or the psychiatric disorder of dual diagnosis patients affects the outcome of the other disorder (Litten & Allen, 1999).

References

- Anthony, J.C., Warner, L.A., & Kessler, R.C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, and controlled substances and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 2, 244–268.
- Batki, S.L., Manfredi, L.B., Jacob, P., & Jones, R.T. (1993). Fluoxetine for cocaine dependence in methadone maintenance: Quantitative plasma and urine cocaine benzoyllecgonine concentrations. *Journal of Clinical Psychopharmacology* 13, 243–250.
- Bowden, C.L., Brugger, A.M., Suann, A.C., Calabrese, J.R., Janicak, P.G., Petty, F., Dilsaver, S.C., Davis, J.M., Rush, A.J., Smally, J.G., Garza-Trevino, E.S., Risch, C., Goodnick, P.J., & Morris, D.D. (1994). Efficacy of divalproex vs. lithium and placebo in the treatment of mania. *Journal of the American Medical Association* 271, 918–924.
- Brady, K.T., Halligan, P., & Malcolm, R.J. (1999). Dual diagnosis. In M. Galanter & H.D. Kleber (eds.), *Textbook of Substance Abuse Treatment*, 2nd ed., Washington, DC: The American Psychiatric Press, pp. 475–483.
- Brady, K.T., Sonne, S.C., Anton, R., & Ballenger, J.C. (1995). Valproate in the treatment of acute bipolar affective episodes complicated by substance abuse: A pilot study. *Journal of Clinical Psychiatry* 56, 118–121.
- Bruno, F. (1989). Buspirone treatment of alcoholic patients. *Psychopathology* 22, 49–59.
- Bukstein, O.G., Glancy, L.J., & Kaminer, Y. (1989). Comorbidity of substance abuse and other psychiatric disorders in adolescents. *American Journal of Psychiatry* 146, 1131–1141.
- Clark, D.B., Parker, A.M., & Lynch, K.G. (1999). Psychopathology and substance-related problems during early adolescence: A survival analysis. *Journal of Clinical Child Psychology* 28, 333–341.
- Clark, D.B., Pollock, N.K., Bukstein, O.G., Mezzich, A.C., Bromberger, J.T., & Donovan, J.E. (1997). Gender and comorbid psychopathology in adolescents with alcohol dependence. *Journal of the American Academy of Child and Adolescent Psychiatry* 36, 1195–1203.
- Cornelius, J.R., Bukstein, O.G., Birmaher, B., Salloum, I.M., Lynch, K., Pollock, N.K., Gershon, S., & Clark, D.B. (2001). Fluoxetine in adolescents with major depression and an alcohol use disorder: An open label trial. *Addictive Behaviors* 26, 735–739.
- Cornelius, J.R., Fabrega, H., Cornelius, M.D., Mezzich J.E., Maher P.J., Salloum, I.M., Thase, M.E., & Ulrich, R.F. (1996). Racial effects on the clinical presentation of alcoholics at a psychiatric hospital. *Comprehensive Psychiatry* 37, 102–108.
- Cornelius, J.R., Jarrett, P.J., Thase, M.E., Fabrega, H., Haas, G.L., Jones-Barlock, J., Mezzich, J.E., & Ulrich, R.F. (1995). Gender effects on the clinical presentation of alcoholics at a psychiatric hospital. *Comprehensive Psychiatry* 36, 1–7.
- Cornelius, J.R., Perkins, K.A., Salloum, I.M., Thase, M.E., & Moss, H.B. (1999). Fluoxetine versus placebo to decrease the smoking of depressed alcoholic patients. *Journal of Clinical Psychopharmacology* 19, 183–184.
- Cornelius, J.R., Pringle, J., Jernigan J., Kirisci, L., & Clark, D.B. (2001). Correlates of mental health service utilization and unmet need among a sample of male adolescents. *Addictive Behaviors* 26, 11–19.

- Cornelius, J.R., Salloum, I.M., Cornelius, M.D., Perel, J.M., Thase, M.E., Ehler, J.G., & Mann, J.J. (1993). Fluoxetine trial in suicidal depressed alcoholics. *Psychopharmacology Bulletin* 29, 195–199.
- Cornelius, J.R., Salloum, I.M., Mezzich, J.E., Cornelius, M.D., Fabrega, H., Ehler, J.G., Ulrich, R.F., Thase, M.E., & Mann, J.J. (1995). Disproportionate suicidality in patients with comorbid major depression and alcoholism. *American Journal of Psychiatry* 152, 358–364.
- Cornelius, J.R., Salloum, I.M., Day, N.L., Thase, M.E., & Mann, J.J. (1996). Patterns of suicidality and alcohol use in alcoholics with major depression. *Alcoholism: Clinical and Experimental Research* 20, 1451–1455.
- Cornelius, J.R., Salloum, I.M., Ehler, J.G., Jarrett, P.J., Cornelius, M.D., Perel, J.M., Thase, M.E., & Black, A. (1997). Fluoxetine in depressed alcoholics: A double-blind, placebo-controlled trial. *Archives of General Psychiatry* 54, 700–705.
- Cornelius, J.R., Salloum, I.M., Thase, M.E., Haskett, R.F., Daley, D.C., Jones-Barlock, A., Upsher, C., & Perel, J.M. (1998). Fluoxetine versus placebo in depressed alcoholic cocaine abusers. *Psychopharmacology Bulletin* 34, 117–121.
- Cornelius, J.R., Salloum, I.M., Haskett, R.F., Ehler, J.G., Jarrett, P.J., Thase, M.E., & Perel, J.M. (1999). Fluoxetine versus placebo for the marijuana use of depressed alcoholics. *Addictive Behaviors* 24, 111–114.
- Cornelius, J.R., Salloum, I.M., Haskett, R.F., Daley, D.C., Cornelius, M.D., Thase, M.E., & Perel, J.M. (2000). Fluoxetine versus placebo in depressed alcoholics: A one-year follow-up study. *Addictive Behaviors* 25, 307–310.
- Cornelius, J.R., Salloum, I.M., Lynch, K., Clark, D.B., & Mann, J.J. (2001). Treating the substance-abusing suicidal patient. In H. Hendin & J.J. Mann (eds.), *The Annals of the New York Academy of Sciences*, 932, 78–93.
- Cornelius, J.R., Thase, M.E., Salloum, I.M., Cornelius, M.D., Black, A., & Mann, J.J. (1998). Cocaine use associated with increased suicidal behavior in depressed alcoholics. *Addictive Behaviors* 23, 119–121.
- Dorus, W., Ostrow, D.G., Anton, R., Cushman, P., Collins, J.F., Schaefer, V., Charles, H.L., Desai, P., Hayashida, M., Malkerneker, U., Willenbring, M., Fiscella, R., & Sather, M.R. (1989). Lithium treatment of depressed and nondepressed alcoholics. *Journal of the American Medical Association* 262, 1646–1652.
- Emslie, G.J., Rush, A.J., Weinberg, W.A., Kowatch, R.A., Hughes, C.W., Carmody, T., & Rintelmann, J. (1997). A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archives of General Psychiatry* 54, 1031–1037.
- Fawcett, J., Clark, D.L., Aagesen, C.A., Pinasi, V.D., Tilkin, J.M., Sellers, D., McGuire, M., & Gibbons, R.D. (1987). A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. *Archives of General Psychiatry* 44, 248–256.
- George, D.T., Rawlings, R., Eckardt, M.J., Phillips, M.J., Shoaf, S.E., & Linnola, M. (1999). Buspirone treatment of alcoholism: Age of onset and cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid concentrations, but not medication treatment, predict return to drinking. *Alcoholism: Clinical and Experimental Research* 23, 272–278.
- Greenfield, S.F., Weiss, R.D., Muenz, L.R., Vagge, L.M., Kelly, J.F., Bello, L.R., & Michael, J. (1998). The effect of depression on return to drinking. *Archives of General Psychiatry* 55, 259–265.
- Helzer, J.E., & Pryzbeck, T.R. (1998). The co-occurrence of alcoholism and other psychiatric disorders in the general population and its impact on treatment. *Journal of Studies on Alcohol* 49, 219–244.
- Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., & Anthony, J.C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Archives of General Psychiatry* 54, 313–321.
- Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., & Kendler, K.S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* 51, 8–19.

- King, C.A., Naylor, M.W., Hill, E.M., Shain, B.N., & Greden, J.F. (1993). Dysthymia characteristic of heavy alcohol use in depressed adolescents. *Biological Psychiatry* 33, 210–212.
- Kranzler, H.R., Burleson, J.A., Del Boca, F.K., Babor, T.F., Korner, P., Brown, J., & Bohn, M. (1994). Buspirone treatment of anxious alcoholics. *Archives of General Psychiatry* 51, 720–731.
- Kranzler, H.R., Burleson, J.A., Korner, P., Del Boca, F.K., Bohn, M.J., Brown, J., & Liebowitz, N. (1995). Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. *American Journal of Psychiatry* 152, 391–397.
- Litten, R.Z., & Allen, J.P. (1995). Pharmacotherapy for alcoholics with collateral depression or anxiety: An update of research findings. *Experimental and Clinical Psychopharmacology* 3, 87–93.
- Litten, R.Z., & Allen, J.P. (1998). Pharmacologic treatment of alcoholics with collateral depression: Issues and future directions. *Psychopharmacology Bulletin* 34, 107–110.
- Litten, R.Z., & Allen, J.P. (1999). Medications for alcohol, illicit drug, and tobacco dependence: An update of research findings. *Journal of Substance Abuse Treatment* 16, 105–112.
- Litten, R.Z., & Fertig, J. (1996). International update: New findings on promising medications. *Alcoholism: Clinical and Experimental Research* 20(Suppl), 216A–218A.
- Malcolm, R., Anton, R.F., Randall, C.L., Johnston, A., Brady, K., & Thevos, A. (1992). A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcoholism: Clinical and Experimental Research* 16, 1007–1013.
- Malec, E., Malec, T., Gagne, M.A., & Dongier, M. (1996). Buspirone in the treatment of alcohol dependence: A placebo-controlled trial. *Alcoholism: Clinical and Experimental Research* 20, 307–312.
- Martin, C.S., Kaczynski, N.A., Maisto, S.A., Bukstein, O.G., & Moss, H.B. (1995). Patterns of DSM-IV alcohol abuse and dependence symptoms in adolescent drinkers. *Journal of Studies on Alcohol* 56, 672–680.
- Mason, B.J., Kocsis, J.H., Ritvo, C.E., & Cutler, R.B. (1996). A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *Journal of the American Medical Association* 275, 761–767.
- McGrath, P.J., Nunes, E.V., Stewart, J.W., Goldman, D., Agosti, V., Ocepek-Welikson, K., & Quitkin, P.M. (1996). Imipramine treatment of alcoholics with major depression: A placebo-controlled clinical trial. *Archives of General Psychiatry* 53, 232–240.
- McLellan, A.T., Luborsky, L., Woody, G.E., O'Brien, C.P., & Druley, K.A. (1983). Predicting response to alcohol and drug abuse treatments. *Archives of General Psychiatry* 40, 620–625.
- Naranjo, C.A., Kadlec, K.E., Sanhueza, P., Woodley-Remus, D., & Sellers, E.M. (1990). Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clinical Pharmacology and Therapeutics* 47, 490–498.
- Nunes, E.V., McGrath, P.F., Quitkin, F.M., Stewart, J.W., Goehl, L., & Ocepek-Welikson, K. (1996). Predictors of antidepressant response in depressed alcoholic patients. *American Journal of Addiction* 5, 308–312.
- O'Malley, S.S., & Carroll, K.M. (1996). Psychotherapeutic considerations in pharmacological trials. *Alcoholism: Clinical and Experimental Research* 20, 17A–22A.
- Paille, F.M., Guelfi, J.D., Perkins, A.C., Royer, R.J., Steru, L., & Parot, P. (1995). Double-blind randomized multicenter trial of acamprosate in maintaining abstinence from alcohol. *Alcohol and Alcoholism* 30, 239–247.
- Powell, B.J., Campbell, J.L., Landon, J.F., Liskou, B.I., Thomas, H.M., Nickel, E.J., Dale, T.M., Penick, E.C., Samuelson, S.D., & Lacoursiere, R.B. (1995). A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. *Alcoholism: Clinical and Experimental Research* 19, 462–468.
- Project MATCH Research Group. (1998). Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcoholism: Clinical and Experimental Research* 22, 1300–1311.
- Regier, D.A., Farmer, M.E., Rae, D.E., Locke, B.Z., Keith, E.J., Judd, L.L., & Goodwin, F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse: Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 264, 2511–2518.

- Riggs, P.D., Mikulich, S.K., Coffman, L.M., & Crowley, T.J. (1997). Fluoxetine in drug-dependent delinquents with major depression: An open trial. *Journal of Child and Adolescent Psychopharmacology* 7, 87-95.
- Roy A. (1998). Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. *Biological Psychiatry* 44, 633-637.
- Salloum, I.M., Cornelius, J.R., Thase, M.E., Daley, D.C., Kirisci, L., & Spotts, C. (1998). Naltrexone utility in depressed alcoholics. *Psychopharmacology Bulletin* 34, 111-115.
- Salloum, I.M., Cornelius, J.R., Mezzich, J.E., Kirisci, L., Daley, D.C., Spotts, C.R., & Zuckoff, A. (2001). Characterizing female bipolar alcoholic patients presenting for initial evaluation. *Addictive Behaviors* 26, 341-348.
- Tollefson, G.D., Montague-Close, J., & Tollefson, S.L. (1992). Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). *Journal of Clinical Psychopharmacology* 12, 19-26.
- Vitiello, B., & Jensen, P.S. (1997). Medication development and testing in children and adolescents. *Archives of General Psychiatry* 54, 871-876.
- Volpicelli, J.R., Alterman, A.I., Hayashida, M., & O'Brien, C.P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49, 876-880.
- Wilkins, J.N. (1997). Pharmacotherapy of schizophrenia patients with comorbid substance abuse. *Schizophrenia Bulletin* 23, 215-228.

Brief Interventions and the Treatment of Alcohol Use Disorders

Current Evidence

Michael F. Fleming

1. Introduction

This brief review of the literature focuses on NIAAA-supported research in brief intervention and brief counseling for treating at-risk, problem, and dependent alcohol use. A number of international studies funded by other sources are also included. An attempt has been made to minimize overlap with research conducted in motivational enhancement and cognitive behavioral therapy.

The goal of brief intervention and brief counseling is to help people reduce or stop their alcohol use. Abstinence may be a long-term goal, but the primary goal of these interventions is to reduce alcohol consumption to low-risk levels and patterns of use.

This report summarizes what we know and what we don't know about brief interventions and brief counseling. The review focuses on research performed in a variety of health care settings, including primary care clinics, hospitals, emergency rooms, and counseling centers. Emphasis is placed on studies that recruited subjects from non-treatment-seeking populations. Studies conducted in research units where subjects were recruited from newspapers or by referral from providers or treatment centers, are not discussed in detail.

This is a very active area of research, and it was difficult to amass current information because much relevant data has yet to be published.

2. Brief Intervention: The Evidence—What We Know and Don't Know

The definition of brief intervention and brief counseling varies across trials and clinical programs, but a number of common elements can be identified:

1. Assessment: "Tell me about your drinking?" "What does your family or partner think about your drinking?" "Have you had any problems related to your alcohol use?" "What do you think about your drinking?" "Have you ever been concerned about how much you drink?"
2. Direct feedback: "As your clinician/therapist, I am concerned about how much you drink and how it is affecting your health." "The car accident is a direct result of your alcohol use." "Your unborn child could develop a birth defect if you continue to drink."
3. Contracting, negotiating, and goal setting: "You need to reduce your drinking. What do you think about cutting down to three drinks two to three times per week?" "I would like you to use these diary cards to keep track of your drinking during the next two weeks. We will review these at your next visit."
4. Behavioral modification techniques: "Here is a list of situations when people drink and sometimes lose control of their drinking. Let's talk about ways you can avoid these situations."
5. Self-help directed bibliotherapy: "*I would like you to review this booklet* and bring it with you at your next visit. It would be very helpful if you would complete some of the exercises in this guide."
6. Follow-up and reinforcement (establishing a plan for supportive phone calls and follow-up visits). "I would like you to schedule a follow-up appointment in 1 month to review your diary cards and answer any questions you might have. I will also ask one of the nurses to call you in a couple of weeks to see how things are going."

The number and duration of sessions vary by trial and setting. The classic brief intervention performed by a physician or nurse usually lasted for 5–10 minutes and was repeated one to three times during a 6–8 week period. Other trials that used therapists or psychologists as the interventionist usually had 30–60 minute counseling sessions for one to six visits. Some trials developed manuals or scripted workbooks. Others studies left it up to the interventionist to decide how to conduct the intervention based on a training program. Some studies used the FRAMES mnemonic developed by Miller as a guide for the intervention (Miller & Sanchez, 1992).

3. What We Know About Brief Intervention!

1. Brief intervention counseling delivered by primary care providers, therapists, and research staff can decrease alcohol use for at least 1 year in nondependent drinkers in primary care clinics, managed care settings, hospitals, and research settings (Bien, Miller, & Tonigan, 1993; Fleming, Manwell, Barry, Adams, & Stauffacher, 1999; Fleming, Mundt, French, Manwell, & Stauffacher, 2002; Gentilrello, Rivara, Donovan, Jurkovich, Daranciang, Dunn, Villaveces, Copass, & Ries, 1999; Kahan, Wilson, & Becker 1995; Marlatt, Baer, Kivlahan, Dimeff, Larimer, Quigley, Somers, & Williams, 1998; Ockene, Adams, Hurley, Wheeler, & Hebert, 1999; Wilk, Jensen, & Havighurst, 1997; WHO, 1996). In positive trials, reductions in alcohol use varied from 10–30% between the experimental and control groups.
2. The effect size for men and women is similar (Fleming, Barry, Manwell, Johnson, & London, 1997; Ockene et al., 1999; Wallace, Cutler, & Haines, 1988; World Health Organization Brief Intervention Study Group, 1996).
3. The effect size for persons over the age of 18 is similar for all age groups including older adults (Fleming et al., 1997, 1999; Marlatt et al., 1998; Monti, Colby, Barnett, Spirito, Rohsenow, Myers, Wollard, & Lewander, 1999; Ockene et al., 1999; Wallace, Cutler, & Haines, 1988; WHO, 1996).
4. Brief intervention can reduce health care use (Fleming et al., 1997; Gentilrello et al., 1999; Israel, Hollander, Sanchez-Craig, Booker, Miller, Gingrich, & Rankin, 1996; Kristenson et al., 1983). Fleming's Project TrEAT (Fleming et al., 1997) and Kristenson et al. (1983) found reductions in emergency room visits and hospital days. Gentilrello et al. (1999) found reductions in hospital readmissions. Israel et al. (1996) reported reductions in physician office visits.
5. Brief intervention can reduce alcohol-related harm. A number of studies found a reduction in laboratory tests such as GGT levels (Kristenson et al., 1983; Israel et al., 1996; Nillsen, 1991; Wallace et al., 1988), sick days (Chick, Lloyd, & Crombie, 1985; Kristenson et al., 1983), and drinking and driving (Fleming et al., (2002); Monti et al., 1999).
6. Brief intervention may reduce mortality (Kristenson et al., 1983; Fleming et al., (2002)). These trials found twice as many deaths in the control group as in the experimental group. Kristenson reported 10 deaths in the control group and 5 in the experimental group 60 months postintervention. Project TrEAT (Fleming et al., (2002)) found 7 deaths in the control group and three in the experimental group during a 48-month postintervention period.
7. Brief intervention may reduce health care and societal costs. An analysis of 12-month outcome data for Project TrEAT found a benefit-cost ratio of 5.6 to 1 for health care and societal costs (Fleming, Mundt, French, Manwell, Stauffacher, & Barry, 2000). Preliminary analysis of the 48-month outcome data for Project TrEAT indicates a benefit-cost

ratio of 3.8 to 1 for health care costs and 39 to 1 for societal costs (Fleming et al., 2002). Costs estimated by Holder, Miller, & Carina (1995), using indirect data, reported a cost saving of 1.5 to 1. Additional cost studies are in progress by several investigators. Data derived from benefit-cost studies are critical because many managed care organizations will not implement alcohol screening and brief intervention until they have compelling evidence that these clinical activities reduce morbidity, mortality, and health care costs.

4. What We Don't Know About Brief Intervention!

1. What are the essential elements—the so-called "black box"—of brief intervention treatment? Is the effect related to assessment, feedback, education, a discussion of norms, cognitive dissonance, contracting, diary cards, bibliotherapy, clinician empathy, discussing cues and alternatives, or follow-up visits? What is the appropriate balance of clinician-directed versus client-centered therapy?
2. Is there a relationship between the number of provider contacts and outcome? A majority of the positive trials included four or more contacts delivered during 6–8 weeks. It isn't clear if additional brief intervention sessions during a longer period would improve efficacy. Project TrEAT (Fleming et al., 2002) found a sustained effect in the experimental group for 48 months with four contacts during an 8-week period. Additional studies are needed.
3. Is there a relationship between the length and complexity of the intervention and outcome? Trials comparing brief intervention to more extensive counseling suggest that minimal benefit is derived from more extensive and complex counseling (Burge, Amodei, Elkin Catala, Andrew, Lane, & Seale, 1997; Wilk et al., 1997; WHO, 1996). Project MATCH (1998) found minimal difference between the MET (Motivational Enhancement Therapy) group and two other arms of the trial that used two to three times as many sessions.
4. Is brief intervention more effective when performed by a member of the patient's personal health care team as opposed to a researcher who does not have a professional relationship with the research subject? Most of the large positive trials used the subject's personal provider to deliver the brief intervention protocol (Anderson & Scott, 1992; Fleming et al., 1997, 1999; Kristenson et al., 1983; Israel et al., 1996; Ockene et al., 1999; Wallace et al., 1988; Wilk et al., 1997). A few trials used researchers with clinical skills to deliver the intervention (Gentilello et al., 1999; Hungerford, Pollock, & Todd, 2000; Marlatt et al., 1998; Monti et al., 1999; WHO, 1996).
5. Does brief intervention increase rates of abstinence before, during, and after pregnancy? Five uncontrolled trials conducted in the 1970s

suggested a treatment effect (Schorling, 1993). Two recent randomized trials conducted by Hankin (1999) and Chang, Wilkins-Haug, Berman, and Goetz (1999) demonstrated minimal differences between control and experimental groups. A number of trials recently funded by the CDC and NIAAA should provide new information in this area. There are gaps in the current research portfolio regarding brief intervention with women in the postpartum period.

6. Does brief intervention reduce rates of adolescent alcohol use? NIAAA-funded trials are in progress to address this question.
7. Does brief intervention reduce alcohol use in persons admitted for trauma? Recently, completed trials have found mixed results. Two different studies conducted at the University of Cincinnati by Sommers and Dyehouse found no effect (Sommers, personal communication). The trial by Gentilello et al. (1999) was positive. Additional trials are in progress.
8. Does brief intervention reduce alcohol use in persons treated in the emergency room? An uncontrolled trial conducted by Hungerford et al. (1999) showed reductions in AUDIT and readiness to change scores. Preliminary data reported by Carty, Longabaugh, Nirenberg, Woolard, Clifford, Sparadeo, and Gogineni (1999) did not reveal significant differences in alcohol use or the DRINC scale at 3 months postintervention. Monti et al. (1999) reported significant decreases in alcohol-related harm but no differences in alcohol use in a sample of older adolescents.
9. What is the efficacy of brief intervention combined with pharmacotherapy? A pilot study conducted by a Yale group found encouraging results (O'Connor, Farren, Rounsaville, & O'Malley, 1997). Project COMBINE should further address this question. Although the Medical Management protocol used by clinicians is more extensive and longer in duration than the majority of brief intervention trials, COMBINE should provide new information in this area.
10. Does brief intervention treatment work with persons who are alcohol-dependent? A number of trials included very heavy drinkers who were probably alcohol-dependent (Wallace et al., 1988; WHO, 1996), but a stratified analysis for this group was not reported. Most of the trials discussed in this review specifically excluded persons who were alcohol-dependent. No trials are currently in progress to address this question. Project MATCH (1998) found no difference between the four-session MET intervention and more extensive counseling delivered to subjects who were alcohol-dependent, but the study did not specifically address this question.
11. Is brief intervention as effective as more intensive and costly specialized treatment for problem drinkers and persons who are alcohol-dependent? No current trials are in progress to specifically address this question. Again, the findings from Project MATCH suggest that four sessions may be as effective as more extensive therapy; however,

this trial did not use group therapy, AA meeting attendance, supportive counseling, or other interventions that are usually part of standard outpatient alcohol treatment.

12. Are there certain groups of patients who are more likely to respond to brief intervention treatment? Completed trials suggest that 60–70% of heavy/problem drinkers do not respond to brief intervention. Project TrEAT found that smokers did not respond as well as nonsmokers (Fleming et al., 1997). TrEAT also found that other covariates such as depression, conduct disorders, and SES factors did not predict a response to brief intervention. Trials have assessed readiness to change and found mixed results (Carty et al., 1999). Much more research needs to be conducted in this area. One of the major problems, however, is the issue of power, sample size, and resources. All but four studies (Fleming et al., 1997; Gentilello et al., 1999; Wallace et al., 1988; WHO, 1996) have had less than 300 subjects per group, and many had less than 100 subjects per cell.
13. How do we implement primary care based screening, brief intervention, and referral in the U.S. health care system? All NIAAA funded trials to date have been *efficacy trials* as opposed to *effectiveness trials*. Studies conducted in Great Britain and in Australia found mixed results. The Phase IN World Health Organization Trial (Gomel, Wutzke, Hardcastle, Lapsley, & Reznik, 1998) attempted to compare three implementation methods: direct mail, telemarketing, and academic detailing. Academic detailing resulted in greater use of the clinical materials distributed than the other methods, but methodological limitations make interpretation of the findings difficult. There have been a number of studies supported by other institutes such as the NCI, NHLBI, AHCPR that provide the alcohol field with a number of potential hypotheses. Strategies that have been found effective include educational programs that include skills training sessions, use of opinion leaders as trainers, personalized performance feedback, financial incentives, computerized reminder systems, academic detailing that includes office based skills training, and policy changes within managed care organizations.
14. How do we develop a "stepped care approach" to treat patients who are adversely affected by alcohol use? How can we develop a continuum of care from primary care to specialized treatment for patients who do not respond to brief intervention? Alcohol treatment programs continue to be separate from general medical care centers and academic medical centers. We need to develop and test better models of care.

5. Methodological Concerns and Challenges

Why have many brief intervention trials found minimal differences between the experimental and control groups?

1. Inadequate sample size. The effect size was robust in many trials, but nearly all trials have found large reductions in alcohol use by control groups. Most trials with less than 100 subjects per group have been negative or equivocal.
2. Spontaneous reductions in alcohol use in control groups. As stated above, nearly all trials demonstrated a reduction in alcohol use by the control group. In most of the negative trials, the controls groups change as much or more than the experimental groups. There are at least four possible reasons: (a) regression to the mean phenomena; (b) historical effects—people reduce their drinking over time due to health, family, societal, work, and cultural factors; (c) the Hawthorne effect—the intervention effect of research procedures; and (d) calling attention to people's drinking may cause them to reduce their use.
3. Failing to mask the intent of the study. Most of the strongly positive trials conducted a partially blinded study. Studies conducted by Fleming et al. (1997, 1999), Gentilello et al. (1999), Israel et al. (1996), Kristenson et al. (1983), Ockene et al. (1999), and Wallace et al. (1988) screened patients using embedded alcohol screening procedures that placed alcohol use in the context of other health issues, such as smoking, exercise, diet, trauma, etc. An attempt was made to blind subjects randomly assigned to the control group to the true nature of the study. For example, in Project TrEAT (Fleming et al., 1997), all baseline and follow-up interview alcohol questions were embedded in a lifestyle survey that also included questions about tobacco use, exercise, weight concerns, mental health issues, and sleep. Many of the studies that did not try to mask the intent of the study were negative or equivocal due to large reductions in alcohol use by control groups.
4. Failure to blind the intervenor to members of the control group. Many successful studies did not inform the clinician which patients were in the control group until the trial was completed. Training and sensitizing clinicians can result in interventions with control subjects.
5. Lack of standardization in the delivery of the intervention protocol by the intervenors. Methodological issues identified in some of the studies include the absence of (a) scripted workbooks or standard protocols, (b) skills training assessments with booster training sessions prior to the first interventions, and (c) quality control procedures to ensure standard delivery across sites and intervenors.
6. Low follow-up rates. Even many of the positive trials report follow-up rates less than 80%. Trials conducted in residency teaching sites, emergency departments, and hospitals have the poorest follow-up rates; community-based primary care sites generally have the highest. The presence of HMOs has influenced the number of persons who change health care providers each year, yet community clinics still have relatively stable patient populations that are easier to follow up. Trials conducted in these settings by Fleming et al. (1997, 1999), Ockene et al.

(1999), and Wallace (1988) report drop-out rates at 1 year of 18, 7, 8, and 15%, respectively. Most studies indicate that follow-up rates are lower in the experimental groups.

7. Use of screening instruments such as the AUDIT, MAST, T-ACE, or Trauma scale to collect baseline and follow-up data as opposed to using time-line follow-up back (TLFB) procedures to obtain better estimates of alcohol use. Some trials randomized subjects based on the results of screening tests. As a result, subjects with no current alcohol use were randomized into the trial. Because alcohol use is the main effect variable in the studies, this significantly limits the power of the trial to detect differences. For example, in the study conducted by Chang et al. (1999) that used a positive score on the T-ACE as the entry criterion, nearly one-half of the pregnant women enrolled in the trial were not drinking any alcohol at the time of randomization. Many trials did not use time-line follow-back procedures or similar methods to assess alcohol use. They estimated use by multiplying the average *frequency* by the average *quantity* reported for a period of time, such as a year, in the case of the AUDIT.

6. Other Methodological Considerations

A number of other methodological issues limit the scientific rigor of many of these trials. These methodological issues include (1) dropping subjects who were randomized but who did not complete one or more intervention sessions, (2) the absence of intention to treat procedures, (3) the failure to blind the researchers conducting the follow-up interviews, and (4) the absence of a laboratory test that is sensitive and specific in a nondependent population.

7. Review of Selected Brief Intervention Trials

The following is detailed review of a limited number of studies:

1. Kristenson et al. (1983): The first large brief intervention trial was conducted in Sweden in the late 1970s as part of a bigger study focusing on the prevention of cardiovascular disease. All males ages 46–53 residing in Malmo, Sweden, were invited to participate in a screening for cardiovascular disease, diabetes, and heavy drinking. Seventy-six percent responded to the invitation. Respondents with GGT levels in the upper 5%, who were also heavy drinkers, were invited to participate in a health behavior study. This study is the only trial to report long-term reductions in hospital days, sick days, and mortality in the experimental group compared to the control group (60 months postrandomization). *The study has a number of strengths* including a community-based sample, blinded conditions, long-term follow-up data, and strong

- outcome measures. *Limitations of the trial* include an all-male sample limited to persons with elevated GGT levels; exclusion in the analysis of controls who sought treatment; an absence of alcohol use outcome data; varying completeness of outcome variables; and an intervention that provided treatment and counseling for a number of health problems, not just alcohol.
2. Wallace et al. (1988): A second important trial, the Medical Research Council trial (MRC), was conducted in Great Britain in the offices of 47 general practitioners. A Health Screening Questionnaire to 70,000 registered patients was mailed or handed. A total of 909 heavy drinkers were randomized into a control or physician-delivered brief intervention group. The intervention included a physician's brief advice to reduce or stop alcohol use, a self-help booklet, weekly diary cards to record alcohol use, and a written contract in the form of a prescription signed by the physician. The follow-up rate at 1 year was 82%. The study found significant reductions in alcohol use and GGT levels between the control and intervention groups in males and a mild reduction in alcohol use in women. As with most brief intervention trials, alcohol use decreased pre- to post in the control group. *The strengths of this trial* include a large sample and effective blinding procedures. The study was also conducted in the offices of general practitioners, thus increasing the generalizability of the findings. *Limitations include* a very high level of alcohol use in the male sample (mean level of alcohol consumption was > 60 drinks/week); an 18% loss to follow-up; a short follow-up period; and an absence of reductions in sick days, morbidity, or health care use.
 3. Anderson and Scott (1992): Anderson and Scott conducted a trial in Oxford, England, to test the effectiveness of a single 10-minute brief advice session with males aged 18–69 who drank more than 20 units of alcohol per week. Subjects were enrolled through a screening program in each physician's office using the self-administered Health Screening Questionnaire (HSQ). A 12-month face-to-face interview assessed alcohol use in the previous 7 days, frequency of binge drinking, consultation rates, and laboratory tests. The drop-out rate was 24% for the experimental group and 36% for the control group. This study demonstrated a significant treatment effect for men in the experimental group. Limitations include a small sample size, a high drop-out rate, and absence of changes in morbidity and use.
 4. WHO (1996): A project sponsored by the World Health Organization (WHO) tested a brief intervention protocol in 10 countries with diverse cultures and health care systems. The goal was to determine if the intervention could demonstrate a reduction in the level of alcohol use and the serious health effects associated with heavy drinking. A total of 1559 subjects (1260 males and 299 females) were randomized to one of three groups. In the core design, Group A (the control group),

received a 20-minute health interview. Group B received the 20-minute health interview, a pamphlet, and a brief 5-minute advice session. A third group, Group C, received the 20-minute health interview and up to three counseling sessions. Follow-up varied with a minimum of 6 months and an average of 9 months. The follow-up rate, which was 75% for the overall study, ranged from 90 to 30%. The study results were positive and demonstrated a significant reduction in alcohol use and binge drinking in the male sample in the two experimental treatment groups, compared to the control group. There were no differences between groups in the female sample. There were no differences in GGT levels or problem scores. *Weaknesses of the trial* include a single follow-up assessment at 9 months, lack of standardized treatment across sites, variation in selection processes across sites, and a high rate of loss to follow-up.

5. Israel et al. (1996): Israel and colleagues conducted a trial in the offices of 42 physicians in a small community in Cambridge, Ontario, Canada. Out of 15,558 adults (ages 30–60) who participated in the screening portion of the trial, 105 met criteria for the trial and were randomized into a brief advice or brief counseling group. The brief advice group received a small self-help booklet and patients were advised to reduce their drinking. The counseling group received six 20-minute counseling sessions with a nurse educator during a 12-month period and a self-help booklet. Published results report data on the 72 patients who participated in the 12-month follow-up survey. Although there were large pre- to postreductions in alcohol use within each of the two groups, the trial reports minimal differences between groups in alcohol use or problem scores at trial end. There was a slight reduction in GGT levels in the experimental male sample. *Study strengths include* a community-based sample and the use of state-of-the-art research procedures. *Limitations include* a small sample size, a 30% loss to follow-up, an absence of a no-treatment control group, and lack of intention to treat procedures.
6. Burge et al. (1997): One of the first community-based U.S. trials was conducted in a family medicine teaching clinic in Texas with a sample of predominantly Mexican-Americans. The trial screened 4014 patients seeking routine care in primary care clinics. A total of 279 of these subjects were randomized into one of four groups: no treatment, patient education only, physician intervention only, and both patient education and physician intervention. Seventy-eight percent of the subjects completed 12-month follow-up procedures that assessed alcohol use, health status, and GGT levels. No significant differences were found among the four groups at follow-up; all groups demonstrated significant improvement in alcohol consumption, ASI variables, and GGT. *Study strengths include* a large ethnic sample and the use of diagnostic interviews for all patients. *Limitations include* small sample sizes

in the four cells, lack of intention to treat procedures (55 subjects randomized to the trial who were lost to follow-up were not included in the analysis), and failure of some subjects in the experimental groups to attend at least one intervention.

7. Fleming et al. (2002): Project TrEAT (Trial for Early Alcohol Treatment) was designed to replicate the Medical Research Council trial (Wallace et al., 1988) conducted in Great Britain. Physicians were recruited through the Wisconsin Research Network, local community hospitals, managed care organizations, and personal contacts. Sixty-four physicians from 17 clinics participated—46 male physicians and 18 female physicians, with a mean age of 46 and a mean of 13 years in practice. A total of 774 men and women ages 18–65 were randomized to a control group or a physician-delivered brief intervention group. Major inclusion criteria included men who drank between 15 and 50 drinks per week, women who drank between 12 and 50 drinks per week, no evidence of alcohol dependence, and no alcohol treatment in the past 12 months.

The major alcohol use outcome variables were average drinks per week, binge drinking, and excessive drinking. Large decreases were found for all alcohol use variables in all groups at 6, 12, 24, 36, and 48 months. The greatest reductions occurred in the female experimental group, where use had decreased by 47% at 12 months (14.8–8.08 drinks/week). The difference between the female intervention and control groups was significant for 7-day alcohol use ($t = 3.7; p < .001$). Men in the experimental group reduced their consumption slightly less than their female counterparts, but large decreases were reported across all alcohol measures. Preliminary analysis suggests a possible treatment effect for days of hospitalization but not for emergency room visits; there was a difference in hospital days at a 48-month follow-up for both men (chi-square = 29.55; $p < .01$) and women (chi-square = 10.98; $p < .05$). *Study limitations* include a failure of 22% of the persons randomized to the experimental group to complete the intervention; an absence of laboratory measures to confirm patient self-report data; and the inability to secure claims data to assess use due to multiple hospitals, emergency rooms, and health care insurance carriers.

8. Marlatt et al. (1998): Marlatt et al. evaluated the efficacy of brief intervention on reducing harmful consequences associated with heavy drinking among high-risk college students. A mailed screening questionnaire was sent to 4000 students who had plans to enroll at the University of Washington in the following term. A total of 2041 students (51%) provided usable questionnaires and indicated a willingness to participate in a research study. A total of 348 high-risk students were selected from this screening pool and randomly assigned to receive an individualized motivational brief intervention in their freshman year of college or to a no-treatment control condition. An additional normative

comparison sample was randomly selected from the pool to provide a natural history comparison ($n = 115$). A total of 379 students (83%) provided data at both the 1- and 2-year follow-up assessments. Although, on average, all high-risk students drank less and reported fewer alcohol-related problems during the 2-year follow-up period, participants who received the brief intervention showed a significantly greater reduction in drinking rates and problems over time compared to participants in the control group. High-risk students in both the intervention and control conditions reported drinking rates and problem consequences that remained substantially greater than students in the normative comparison sample throughout the follow-up period. *Study strengths included* screening during the final months of high school to avoid contamination by further assessments once students arrived on campus, a large sample size with a balance of men and women, random assignment to conditions, and inclusion of a normative comparison sample to assess developmental trends in drinking and problems. *Limitations include* a lack of process measures to account for change in drinking rates and problems, reliance on self-report data, and the possibility that this sample of high-risk drinkers may not generalize to other college student populations.

9. Fleming et al. (1999): Project GOAL (Guiding Older Adult Lifestyles) was designed to test the efficacy of brief physician advice in older adult problem drinkers over the age of 65. This is one of the first brief intervention trial focused on older adults. Forty-three physicians from 24 community-based primary care practices located in 10 Wisconsin counties were recruited and trained. Of the 6073 patients screened for problem drinking, 105 males and 53 females met inclusion criteria ($n = 158$) and were randomized to a control ($n = 71$) or intervention group ($n = 87$). One hundred forty-six subjects (92.4%) participated in the 12-month follow-up procedures. The 12-month follow-up data indicate a significant reduction in 7-day alcohol use ($t = 3.77; p < .001$), episodes of binge drinking ($t = 2.68; p < .005$), and frequency of excessive drinking ($t = 2.65; p < .005$). This is one of the few brief intervention trials where the control group exhibited no pre- to postrandomization changes in drinking. No significant changes in health status were demonstrated; there were too few use events at 12 months to estimate differences between groups. *Study limitations include* a small sample size, a large number of practitioners performing the intervention that made quality control more difficult, and a lack of reduction in alcohol-related consequences.
10. Chang et al. (1999): Chang et al. screened 1165 pregnant women using a health screening survey containing the TACE in a prenatal clinic at a large teaching hospital in Boston. Two hundred-fifty women were randomized to a brief intervention or assessment only group. The outcome measures of interest were assessed during the postpartum period.

There were pre- to postrandomization reductions in alcohol use in both groups, but there were no differences in alcohol use between groups. *Study strengths* include a large sample of pregnant women and a standardized treatment procedure. Methodological weaknesses include low rates of alcohol use, lengthy assessment and follow-up procedures, and a single follow-up interview.

11. Monti et al. (1999): Monti et al. evaluated the use of a brief motivational intervention to reduce alcohol-related consequences and use among adolescents treated in an emergency room following an alcohol-related event. Ninety-four patients 18–19 years old were randomly assigned to receive either a 35–40 minute motivational intervention from a research interventionist or standard care. Follow-up assessments at 3 and 6 months showed that patients in the intervention group had a significantly lower incidence of drinking and driving, traffic violations, alcohol-related injuries, and alcohol-related problems than patients in the standard care group. Both conditions showed reduced consumption during follow-up, particularly during the first 3 months. *Study limitations* include a high refusal rate (33.4%), short-term follow-up, and the generalizability of the results to older adolescents and young adults.
12. Carty et al. (1999): Carty et al. assessed the efficacy of brief intervention on alcohol-related outcomes for adults presenting in the emergency room for injury treatment. A total of 261 subjects who screened positive according to the AUDIT or by breathalyzer test were randomly assigned to one of three treatment conditions: standard care, standard care plus brief intervention, or standard care with brief intervention and a booster session 7–10 days later. A total of 92% of the subjects participated in a month follow-up assessment that included the AUDIT, the DrInC, and an Injury Behavior Checklist. No difference was found in alcohol consumption among the groups. Patients who received the combination of a brief and booster session reported fewer negative consequence than either the standard care or brief intervention alone groups. Further analyses indicate that a combination of brief intervention and a booster session within 7–10 days may be especially effective for those patients who report no motivation to change their drinking prior to the intervention. *Study limitations* include a failure to use intention to treat analyses, a small number of participants in each cell, and a short follow-up period.
13. Gentilello et al. (1999): Gentilello et al. studied the efficacy of providing brief alcohol interventions as a routine with trauma care to reduce alcohol consumption and decrease trauma recidivism. A total of 2524 patients at a level I trauma center for treatment of an injury were screened for an alcohol problem via BA and the SMAST. Those with positive results were randomized to a brief intervention ($n = 36$) control group ($n = 396$). The intervention, conducted on or near the day

of hospital discharge, was a single motivational interview with a trained psychologist. Subjects were interviewed at months to assess changes in alcohol use. Trauma registries and Washington State databases were used to assess rates of hospital readmission and legal events. The investigators reported significant reductions in alcohol use 12-months postintervention, compared to the control. W1 was a reduction in trauma events and readmission; these differences were not statistically significant. *Limitations of the trial include* (a) 17% of intervention subjects did not receive the intervention, (b) follow-up rates at 12 months were 54%, (c) the report used the AUDIT quantity-frequency questions to assess weekly alcohol use instead of TLFB procedures, (d) only 45% of the control group participated in the baseline data assessment, (e) baseline levels of alcohol use and binge drinking were not reported, and (f) utilization and legal events were not statistically significant.

8. Recommendations

A number of gaps have been identified in our knowledge base. Additional research seems appropriate in the following areas:

- What is the benefit–cost of screening, brief intervention, and referral?
- Does brief intervention reduce morbidity, mortality, and societal costs?
- What is the efficacy of brief intervention for adolescents, women, pregnant women, women in the postpartum period, non-Caucasian persons, and older adults?
- What are the key therapeutic elements of brief intervention?
- How do we help people who do not respond to brief intervention?
- How many sessions, for what period of time, and at what intensity are necessary to effect a change?
- What are the key cofactors that influence patient response to brief intervention (e.g., depression, anxiety, conduct disorder, PTSD, smoking status, illicit drug use, partner use, readiness to change status, clinician empathy)?
- Can brief intervention reduce alcohol-related domestic violence?
- What is the efficacy of brief intervention when delivered by a computer, telephone, or over the Internet?
- How do we implement screening, brief intervention, and referral in the U.S. health care system?
- How do we integrate alcohol prevention activities in the context of other preventive initiatives such as cancer and heart disease prevention programs?
- How do we change public policy and reimbursement mechanisms to support screening, brief intervention, and referral in medical settings?

References

- Anderson, P., & Scott, E. (1992). The effect of general practitioners' advice to heavy drinking men. *British Journal of Addiction* 87, 891–900.
- Bien, T.H., Miller, W.R., & Tonigan, J.S. (1993). Brief interventions for alcohol problems: A review. *Addiction* 88, 315–335.
- Burge, S.K., Amodei, N., Elkin, B., Catala, S., Andrew, S.R., Lane, P.A., & Seale, J.P. (1997). An evaluation of two primary care interventions for alcohol abuse among Mexican-American patients. *Addiction* 92, 1705–1716.
- Carty, K.A., Longabaugh, R., Nirenberg, T., Woolard, R., Clifford, P., Sparadeo, F., & Gogineni, A. (1999). Three month drinking related outcomes for subcritically injured alcohol positive patients receiving a brief motivational intervention. *Research Society on Alcoholism*, Santa Barbara, CA, June 28.
- Chang, G., Wilkins-Haug, L., Berman, S., & Goetz, M.A. (1999). Brief intervention for alcohol use in pregnancy, randomized trial. *Addiction* 94, 1499–1508.
- Chick, J., Lloyd, G., & Crombie, E. (1985). Counseling problem drinkers in medical wards: A controlled study. *British Medical Journal of Clinical Research Education* 290, 965–967.
- Fleming, M.F., Barry, K.L., Manwell, L.B., Johnson, K., & London, R. (1997). Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices. *Journal of the American Medical Association* 277, 1039–1045.
- Fleming, M.F., Manwell, L.B., Barry, K.L., Adams, W., & Stauffacher, E.A. (1999). Brief physician advice for alcohol problems in older adults: A randomized community-based trial. *The Journal of Family Practice* 48, 378–384.
- Fleming, M.F., Mundt, M.P., French, M.T., Manwell, L.B., Stauffacher, E.A., & Barry, K.L. (2000). Benefit–cost analysis of brief physician advice with problem drinkers in primary care settings. *Medical Care* 38, 7–18.
- Fleming, M.F., Mundt, M.P., French, M.T., Manwell, L.B., & Stauffacher, E.A. (2002). Project TrEAT, a trial for early alcohol treatment: 4-year follow-up. *Alcoholism, Clinical and Experimental Research* 26(1), 36–42.
- Gentilello, L.M., Rivara, F.P., Donovan, D.M., Jurkovich, G.J., Daranciang, E., Dunn, C.W., Villaveces, A., Copass, M., & Ries, R.R. (1999). Alcohol interventions in a trauma center as a means of reducing the risk of injury recurrence. *Annals of Surgery* 230, 473–480.
- Gomel, M.K., Wutzke, S.E., Hardcastle, D.M., Lapsley, H., & Reznik, R.B. (1998). Cost-effectiveness of strategies to market and train primary health care physicians in brief intervention techniques for hazardous alcohol use. *Social Science Medicine* 47, 203–211.
- Hankin, J., personal communication, 1999.
- Holder, H.D., Miller, T.R., & Carina, R.T. (1995). *Cost Savings of Substance Abuse Prevention in Managed Care*. Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Prevention.
- Hungerford, D.W., Pollock, D.A., & Todd, K.H. (2000). Acceptability of emergency department-based screening and brief intervention for alcohol problems. *Academic Emergency Medicine* 7, 1383–1392.
- Israel, Y., Hollander, O., Sanchez-Craig, M., Booker, S., Miller, V., Gingrich, R., & Rankin, J.G. (1996). Screening for problem drinking and counseling by the primary care physician-nurse team. *Alcoholism, Clinical and Experimental Research* 20, 1443–1450.
- Kahan, M., Wilson, L., & Becker, L. (1995). Effectiveness of physician-based interventions with problem drinkers: A review. *Canadian Medical Associate Journal* 152, 851–859.
- Kristenson, H., Ohlin, H., Hulten-Nosslien, M.B., Trell, E., & Hood, B. (1983). Identification and intervention of heavy drinking in middle-aged men: Results and follow-up of 24–60 months of long-term study with randomized controls. *Alcoholism, Clinical and Experimental Research* 7, 203–209.
- Marlatt, G.A., Baer, J.S., Kivlahan, D.R., Dimeff, L.A., Larimer, M.E., Quigley, L.A., Somers, J.M., & Williams, E. (1998). Screening and brief intervention for high-risk college student drinkers: Results from a 2-year follow-up assessment. *Journal Consult Clinical Psychology* 66, 604–615.

- Miller, W.R., & Sanchez, V.C. (1992). Motivating young adults for treatment and lifestyle change. In G. Howard (ed.), *Issues in Alcohol Use and Misuse in Young Adults*. Notre Dame, IN: University of Notre Dame Press.
- Monti, P.M., Colby, S.M., Barnett, N.P., Spirito, A., Rohsenow, D.J., Myers, M., Wollard, R., & Lewander, W. (1999). Brief intervention for harm reduction with alcohol-positive older adolescents in a hospital emergency department. *Consult Clinical Psychologist* 67, 989–994.
- Nilssen, O. (1991). The Tromso study: Identification of and a controlled intervention on a population of early-stage risk drinkers. *Preventive Medicine* 20, 518–528.
- Ockene, J.K., Adams, A., Hurley, T.G., Wheeler, E.V., & Hebert, J.R. (1999). Brief physician- and nurse practitioner-delivered counseling for high risk drinkers: Does it work? *Archives of Internal Medicine* 159, 2198–2205.
- O'Connor, P.G., Farren, C.K., Rounsville, B.J., & O'Malley, S.S. (1997). A preliminary investigation of the management of alcohol dependence with naltrexone by primary care providers. *The American Journal of Medicine* 103, 477–482.
- Project MATCH Research Group. (1998). Matching alcoholism treatments to client heterogeneity: Treatment main effects and matching effects on drinking during treatment. *Journal of Studies on Alcohol* 59, 631–639.
- Schorling, J.B. (1993). The prevention of prenatal alcohol use: A critical analysis of intervention studies. *Journal of Studies on Alcohol* 54, 261–267.
- Senft, R.A., Polen, M.R., Freeborn, D.K., & Hollis, J.F. (1997). Brief intervention in a primary care setting for hazardous drinkers. *American Journal of Preventive Medicine* 13, 464–470.
- Wallace, P., Cutler, S., & Haines, A. (1988). Randomized controlled trial of general practitioner intervention in patients with excessive alcohol consumption. *British Medical Journal* 297, 663–668.
- Wilk, A.L., Jensen, N.M., & Havighurst, T.C. (1997). Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. *Journal of General Internal Medicine* 12, 274–283.
- World Health Organization Brief Intervention Study Group. (1996). A cross-national trial of brief interventions with heavy drinkers. *American Journal of Public Health* 86, 948–955.

Spirituality, Treatment, and Recovery

William R. Miller

1. Defining Spirituality

Spirituality, the subject of this chapter, is notoriously difficult to delimit. For individuals, its meaning varies widely, but for scientific purposes, a consistent and replicable definition is needed. Just when you think that you have a neat operational fence around spirituality, it breaks loose, refusing to be corralled.

There are, of course, common and dictionary meanings. That which is spiritual is often defined in contrast to what it is not: material. Spirituality has to do with that which transcends material reality. One need not affirm the reality of a metaphysical plane apart from the physical world to be curious about the aspects of human nature that are called "spiritual" and their impact on material phenomena such as alcohol use. To study this domain, however, one does need a working model.

During the past 5 years, several expert committees have grappled with a scientific conception of spirituality (Larson, Swyers, & McCullough, 1998; Miller & Thoresen, 2001; National Institute on Alcohol Abuse and Alcoholism, 1999). Here, briefly, are the emergent working assumptions, admittedly debatable, that served as background for the development of this chapter:

1. Spirituality is not interchangeable with religion. Religion is a social phenomenon, defined by its boundaries (e.g., membership, beliefs, prescribed and proscribed practices). Spirituality is one principal area of concern for religion, but religions also have other nonspiritual goals and purposes. Because these concepts overlap, we will also use the combined term "religious/spiritual" (abbreviated R/S) in our discussion.
2. Spirituality is best understood as characteristic of individuals. It includes the individual's "religion" or religiousness but is not defined

in relation to religion. One's spirituality may, in fact, be either enhanced or impaired by experience with religion.

3. Spirituality is not a commodity that is present or absent, or one that is possessed in amount. Rather it is a complex latent construct, like personality or mental health.
4. As a latent construct, spirituality is multidimensional. Just as personality or mental health cannot be adequately represented by a single measure or dimension, spirituality is best understood as comprised of multiple dimensions including (a) behavior and practices, (b) beliefs, (c) motivations and values, and (d) subjective experience. Each of these dimensions itself encompasses multiple components.
5. As with personality, every person can be located somewhere within the multidimensional space of spirituality. Therefore, it is not useful to characterize individuals as "more" or "less" spiritual than others. The assessment of spirituality has to do with understanding the person's location along these multiple dimensions.

2. Spirituality and Alcoholism

There is something remarkable about the alcoholism field. During the latter half of the twentieth century, treatment of virtually all medical and psychological problems was secularized. Within mainstream Western psychology and medicine, spirituality was largely relegated to the realm of superstition or last resort. For the first time in thousands of years of recorded history, it became normative for healing to separate spirit from both body and mind. Alcoholism is a notable exception, an area where the importance of spirituality has never been lost but has retained a significant and sometimes central role in understanding the process of recovery. The alcoholism field has been like a monastery, preserving vital insights through the Middle Ages of medicine and psychology.

Much of the reason for this, of course, can be found in the international fellowship of Alcoholics Anonymous (AA) and its 12-step kin. Within AA, spirituality is regarded not merely as a piece of a puzzle, but as the puzzle itself, playing a central role in the development of and recovery from alcoholism. The etiology of alcoholism is understood as encompassing body, mind, and spirit, but is discussed in the "big book" (Alcoholics Anonymous, 1976) as a problem of character, of ego run amok. The 12 steps make no mention of disease, denial, neurotransmitters, or self-control. Instead they emphasize contact with God, humility, prayer and meditation, taking personal moral inventory, and serving others (Kurtz, 1988; Tonigan, Toscova, & Connors, 1999).

The testimony of AA is not the only evidence for a link between alcohol and spirituality. There is the interesting phenomenon that world religions are seldom silent or neutral on the subject of alcohol. Some religions (e.g., Islam, Mormonism) prohibit any use of alcohol. Followers of such religions are, of

course, much more likely to be abstainers, but among those who do drink, the risk of heavy drinking, problems, and dependence may be higher than that for drinkers in the general population. Other religions (e.g., Judaism, Christianity) incorporate alcohol into their most central and sacred rituals. The official policy of the Presbyterian Church affirms both abstinence and drinking as valid life choices but condemns as sinful the use of alcohol in a manner that inflicts harm or risk of harm on oneself or others (Task Force on the Social and Health Effects of Alcohol Use and Abuse, 1986).

One of the most consistent empirical findings in alcohol research (though one seldom reported in textbooks) is the inverse relationship between religious/spiritual (R/S) involvement and alcohol problems (Miller & Bennett, 1998). Scores of studies document this predictive relationship. R/S involvement predicts a low level of concurrent and subsequent alcohol use, problems, and dependence. Conversely, alcohol use disorders are often associated with a low level of R/S involvement. The correlation is observed even when relatively weak (often single-item) R/S measures have been used.

Why this inverse relationship? Correlation is not causation, and the reasons for this widely replicated finding need to be clarified. From longitudinal research, it is clear that R/S is often a prospective predictor of alcohol use and problems. In this statistical sense, R/S involvement is a protective factor, and low religiousness is a risk factor for alcohol use disorders. It is possible, however, that some third factor is responsible for both R/S and alcohol risk. The Minnesota twin study, for example, reported a relatively high heritability ratio for religiousness (Waller, Kojetin, Bouchard, Lykken, & Tellegen, 1990), and it is conceivable that common genetic and/or personality factors predispose people to be more religious and to avoid the problematic use of alcohol. Religious parents may raise children who are both more likely to be religious and less likely to abuse alcohol.

There is also an unanswered question as to what variables mediate or moderate the relationship between R/S and drinking. George Ellison and Larson (in press), for example, reviewed evidence as to whether decreased rates of mental disorders among more religious individuals could be explained by the higher level of social support often observed within religious communities. Social support accounted for part of the protective relationship, but R/S continued to predict mental health independent of the influence of social support. R/S affiliation, practices, beliefs, values, or experiences may indirectly decrease risk by reducing other known risk factors for alcohol abuse, such as cigarette smoking or associating with antisocial or substance-abusing peers.

It is also quite plausible that influence flows in both directions: that alcohol abuse conflicts with and diminishes R/S involvement. *Spiritus contra spiritum*, Carl Jung observed, alcohol (spirits) and spirituality are mutually inhibitory. Religions often enjoin their adherents to refrain from using alcohol for spiritual reasons—if not entirely, then during certain holy times of fasting. A defining characteristic of alcohol dependence is that drinking gradually displaces and takes priority over everything else—a classic expression of idolatry.

It is an interesting subject for future research to study acute and chronic effects of alcohol use on spiritual dependent variables: on R/S practices, beliefs, values, and experiences.

3. Spirituality and Recovery

If *spiritus contra spiritum* holds true, then one might expect that recovery from alcoholism is paralleled by spiritual growth. Indeed, within the program of AA, spiritual maturation is regarded as an essential component of recovery that displaces the centrality of alcohol and ego. This is reflected in the upward recovery slope of the classic U-shaped curve drawn by Max Glatt, based on Jellinek's (1952) survey of AA members.

Longitudinal study is needed here to clarify R/S changes that accompany stable recovery. There is some evidence that core guiding values change markedly during the course of recovery, away from egocentric and toward more spiritually rooted goals (Brown & Peterson, 1990; Miller & Cde Baca, 1994, 2001). The sense of meaning and purpose in life is often at a low ebb during alcohol dependence and tends to increase during recovery (Tonigan, Miller, & Connors, 2001). Venner and Miller (2001) compared the development of and recovery from alcoholism among Navajo people with the progression of symptoms described by Jellinek (1952). They found that the emergence of "vague spiritual desires" was much earlier in their sample and that prayer was the first change effort. The role of spirituality in recovery may also be clarified by studying the rapid transformational changes described in AA as "spiritual awakening." Dr. William Silk worm (Alcoholics Anonymous, 1976, p. 27) described them as "huge emotional displacements and rearrangements. Ideas, emotions, and attitudes which were once the guiding forces of the lives of these men are suddenly cast to one side, and a completely new set of conceptions and motives begin to dominate them." The experience of AA's cofounder, Bill W., is a clear example:

My depression deepened unbearably and finally it seemed to me as though I were at the bottom of the pit. I still gagged badly on the notion of a Power greater than myself, but finally, just for a moment, the last vestige of my proud obstinacy was crushed. All at once I found myself crying out, "If there is a God, let Him show Himself! I am ready to do anything, anything!" Suddenly the room lit up with a great white light. I was caught up into an ecstasy which there are no words to describe. It seemed to me, in the mind's eye, that I was on a mountain and that a wind not of air but of spirit was blowing. And then it burst upon me that I was a free man. (Kurtz, 1988, pp. 19–20)

Such real-life "quantum changes" may happen much more frequently than is often assumed, and they appear to have common form and content (Miller & C'de Baca, 2001). Many contain classic elements of a mystical experience, and it is common for alcohol-dependent people who have such an experience to report a sudden, permanent cessation of drinking with abrupt and complete

loss of craving and urges. Such transformations are often associated with rapid and stable changes in self-concept, values, *Weltanschauung*, affect, and personality.

4. Spirituality and Treatment

4.1. AA and Treatment

The fellowship and program of AA are sometimes confused with treatment programs that lay claim to a 12-step approach. Through the 12 steps, the program of AA offers a broad method for living, offered free of charge. AA clearly differentiates itself from both treatment and religion. Unlike treatment, it is not time-limited; it has no clear end or discharge. No professionals deliver interventions to patients, and no fees are charged. It is not limited to office hours and is available in many areas 24 hours a day every day.

Within a Minnesota model of treatment (Laundergan, 1982), the spiritual focus of AA has been mixed with and often overshadowed by a predispositional disease model, promulgating beliefs and practices that are not inherent in, and in some cases are inconsistent with the AA program (Miller & Hester, 2003; Miller & Kurtz, 1994). Consider, for example, the common assertion that alcoholism is fundamentally a biological disorder, a genetically based metabolic and brain disease that renders the individual physically incapable of moderate drinking. AA takes no such stand on the etiology of alcoholism and offers instead an unambiguously spiritual program reflected in its 12 steps. Some disease model proponents have castigated AA for implying that spirit, character, or will have anything to do with alcoholism (Milam & Ketcham, 1983). If spirituality is addressed at all in treatment (other than referring clients to AA), it is often consigned to a minor ancillary role much like that of the chaplain in a large public hospital.

It has also been common in U.S. treatment to identify clients as "alcoholic" and "in denial," placing great emphasis on their public acknowledgment of this label. Despite adverse evidence from outcome research (Miller & Wilbourne, 2002), treatment has often been quite confrontational in focus, pressing clients to accept not only the designation "alcoholic" but also a predispositional disease explanation of its etiology. None of this is grounded or found in the big book of AA. To the contrary, Bill W.'s well-known chapter on "Working with Others" commends gentle patience rather than confrontation, and the label "alcoholic" is one that is never to be imposed on someone else. So far did treatment, in the name of a 12-step approach, digress from the original spirit and program of AA, as described by its founders (Kurtz, 1988; Miller & Kurtz, 1994).

In fairness, there has been a significant turning of this tide. The Hazelden Foundation (1985), the flagship program of the Minnesota model, publicly renounced aggressive confrontation two decades ago, expressing regret that such methods had come to be associated with a Minnesota model and espousing a kinder, gentler approach. Recent manuals of Twelve-Step Facilitation

(TSF) therapy place greater emphasis on the spiritual program of AA and retain some traditional tenets of a predispositional disease model (Nowinski, Baker, & Carroll, 1992). Nevertheless, the authoritarian excesses of a confrontational approach, epitomized in Synanon-based therapeutic communities (Yablonsky, 1965, 1989), continue to be found in practice (Shavelson, 2001) and stand in stark contrast to the humble companion way of Bill W.

4.2. AA and Treatment Outcome

In the United States, at least, both pretreatment and posttreatment AA attendance is common among alcohol-dependent clients (Tonigan, Connors, & Miller, in press). Regardless of the treatment approach being delivered, it is likely that one-third to one-half of clients or more have already been to AA and are likely to attend during or after treatment. Although AA is not treatment, it is perilous to overlook its potential impact on outcomes. It is widely replicated that AA engagement during and after either inpatient or outpatient treatment is positively associated with abstinence outcomes, particularly continuous abstinence (Tonigan, Connors, & Miller, in press; Tonigan & Toscova, 1998). Most often, such engagement has been measured as frequency of attendance at AA meetings. When AA *involvement* is measured (e.g., working the 12 steps, reading AA materials, having or being a sponsor), the positive relationship tends to be stronger (Horstmann & Tonigan, 2000; Montgomery, Miller, & Tonigan, 1995).

There is reason, then, to encourage clients to sample and attend 12-step meetings. It is common for people being treated for alcohol use disorders to report having had bad experiences with AA or religion that led to disaffiliation. (After all, if it had worked for them, they would not be in treatment.) As with churches and worship services, there is usually wide variability in the nature of AA meetings within a geographic area (Tonigan, Ashcroft, & Miller, 1995), and this variety permits individuals to seek meetings more to their liking. Ultimately, of course, people decide for themselves. We follow Glaser's (1993) recommendation that all clients should be encouraged to try AA, but none should be required to do so.

This raises another important issue. From its beginning, AA was designed to work by voluntary attraction, not coercion. The practice of *requiring* people (e.g., as part of treatment, employment, or court order) to attend AA is, we believe, as inappropriate as requiring them to attend worship services, for at least three reasons. First, it violates the fundamental nature of AA, and it may also violate civil rights. Second, studies of mandatory AA attendance have found no beneficial effect on drinking outcomes (Miller & Wilbourne, 2002). Third, there are sound psychological reasons to expect that temporary coercion could undermine intrinsic motivation to participate voluntarily in AA after the requirement has been lifted (Brehm & Brehm, 1981; Deci, 1985). Although this issue has not yet been studied, it is plausible that coerced attendance at AA may actually inoculate against later voluntary attraction and affiliation, thereby depriving people of any attendant benefits.

There are, however, systematic encouragement procedures that can be used to enhance voluntary AA attendance. Among clients in a study by Sisson and Mallams (1981) who were given "systematic encouragement" to attend AA, 100% got to a meeting. Among those simply referred to AA and given a list of local meetings, none attended a meeting. The systematic encouragement procedure included putting the client in contact with an AA member who offered to provide transportation and accompany the person to his or her first meeting.

4.3. Twelve-Step Facilitation (TSF) Therapy

Although, as discussed above, programs have long described themselves as offering "12-step treatment," only recently have such treatments been evaluated in clinical trials. Keso and Salaspuro (1990) compared a Minnesota (Hazelden) model inpatient program with a traditional Finnish model of treatment and found no between-program difference in overall alcohol consumption. For the 8–12 month interval only, they observed a significantly ($p < .05$) higher rate of abstinence in the Hazelden group (26% vs. 10%). With a lower rate of controlled drinking outcomes in the Hazelden group (11% vs. 18% for months 8–12), the overall rate of favorable outcomes (abstinent or controlled drinking) did not differ at any follow-up point. Rates of continuous abstinence for 12 months after treatment (14% vs. 2%) were also significantly different. As discussed earlier, the Minnesota model combines 12-step principles with disease-model education and therapeutic methods that are not derived from the AA program, and it is, therefore, difficult to infer the contribution of spiritual components to such treatment outcomes.

A treatment method more closely and exclusively based on the AA program is Twelve-Step Facilitation (TSF) therapy, originally developed for Project MATCH (1993; Nowinski et al., 1992). TSF was designed as a 12-session outpatient psychotherapy explicitly focused on the 12-step program and intended to involve clients in AA. A total of 1726 clients were randomly assigned to TSF, cognitive-behavior therapy, or motivational enhancement therapy. Although the three treatments did not differ on outcomes during the 12 months after treatment, as measured by two *a priori* measures of drinking (percent days abstinent and drinks per drinking day), the percentage of outpatients who remained completely abstinent was eleven percentage points higher in the TSF group, a difference that persisted at follow-up 3 years after treatment (Project MATCH, 1997, 1998).

As expected, TSF also significantly increased AA attendance during and after treatment. The rate of AA attendance diminished among TSF clients after treatment, however, until at 12 months it was no longer significantly higher than in the other two treatment conditions. Curiously, although frequency of meeting attendance decreased substantially among TSF clients, AA *involvement* did not, that is, TSF clients reported that they continued to practice the program of AA despite diminished or even discontinued attendance. The beneficial outcomes of TSF for 3 years were not undermined by diminished frequency of

AA attendance. This suggests the possibility of a gradual internalization of the 12-step program.

A parallel comparison was provided in a naturalistic study of alcohol treatment programs offered in Veterans Administration (VA) Medical Centers (Ouimette, Finney, & Moos, 1997). This study was not a randomized trial and did not use standardized manual-guided treatments. Instead, VA alcohol treatment programs were characterized as working within a 12-step, cognitive-behavioral, or mixed model (combining both). Among 3018 patients treated in these programs, a significantly higher percentage (26%) in 12-step programs abstained completely for at least 12 months after treatment, compared with 19% in the other two types of programs.

In a randomized clinical trial conducted at the University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions (CASAA), we compared TSF with a community reinforcement approach (CRA) for clients who had initially refused treatment but were persuaded by their loved ones to seek help (Miller, Meyers, Tonigan, & Grant, 2001). Similar to the findings of prior studies, clients randomly assigned to TSF showed large reductions in drinking that were equal in magnitude to those from CRA, which is itself a treatment approach with strong evidence of efficacy from randomized clinical trials (Meyers & Miller, 2001). Once again, a 12-step focused treatment yielded reductions in alcohol consumption as good as those from a well-established cognitive-behavioral approach. During the first 6 months, those in the TSF groups reported a higher rate of complete abstinence (51%) compared to those in the CRA groups (33%), a difference no longer present in months 7–12.

There are noteworthy similarities in the findings of the four separate studies just reviewed, all conducted by different research groups. In all four, treatment emphasizing a 12-step approach yielded significantly higher rates of continuous abstinence during some period of follow-up. Overall reductions in drinking with a TSF approach were comparable at most or all follow-up points to those with other (primarily cognitive-behavioral) treatment approaches.

It is important to note that treatment programs designated as "disease model" vary widely in the extent to which they emphasize the spiritual steps of AA. Milam and Ketcham (1983), for example, advocated a biogenetic disease model but explicitly distanced themselves from the moral/spiritual precepts of AA. In an earlier clinical trial conducted at CASAA, we compared CRA with a traditional disease model outpatient treatment that encouraged AA attendance but gave little or no emphasis to 12-step spirituality (Miller et al., 2001). In this study, CRA yielded significantly better outcomes than those of traditional treatment. In evaluating treatment programs designated as "traditional," "disease model," "Minnesota model," or even "Twelve-Step," it is important to specify the extent and manner in which the spiritual elements of AA are implemented. It is possible that the effectiveness of such programs is related to the degree of emphasis on the spiritual aspects of the AA program.

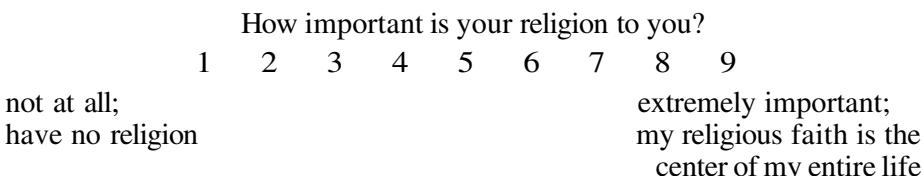
In sum, there is strong evidence from clinical trials that TSF yields outcomes at least as favorable as those of state-of-the-art cognitive-behavioral

treatment, findings paralleled in a large quasi-experimental naturalistic study of treatment. A sensible next step in understanding the efficacy of TSF would be to include appropriate spiritual process measures to determine what changes in spirituality occur through AA involvement and how those are related to sobriety.

4.4. Beyond 12-Step Spirituality

A 12-step approach is not, of course, the only way in which spirituality can be addressed in treating alcohol use disorders. Various authors have explored broader spiritual aspects of addiction (e.g. Kurtz & Ketcham, 1992; May, 1991). No other spiritual perspective has been so well developed or evaluated as the 12-step approach, but many other avenues could be explored.

4.4.1. Spiritual Assessment. A basic first step, as described above, would be to include a reliable assessment of spirituality in pretreatment and posttreatment evaluation, a practice that has already been required, at least in principle, by the U.S. Joint Commission on Accreditation of Healthcare Organizations. A brief or more thorough R/S history could be included in an intake clinical interview, depending upon the interviewer's expertise and training (Pruyser, 1976). If brevity is essential, there are several useful and well-tested single items that can be incorporated verbatim in an intake questionnaire (Gorsuch & Miller, 1999), such as,



Psychologists of religion have also developed and validated a wide range of R/S questionnaires (Hill & Hood, 1999). An excellent multidimensional paper-and-pencil instrument has been developed by the U.S. National Institute on Aging in collaboration with the Fetzer Institute (1999). Such self-administered questionnaires can be included at low cost in treatment assessment protocols.

4.4.2. Reengagement. Often, people who sought treatment for alcohol problems were once involved with a religious tradition but for various reasons (including their excessive drinking), became disengaged. Becoming detached from former healthy activities and interests is a hallmark of alcohol dependence. Clients with a history of religious involvement can be encouraged to renew affiliation, much as we encourage them to attend AA. Systematic procedures that have been used successfully to encourage sampling of AA or other community activities (Meyers & Smith, 1995) can also be used to enhance reaffiliation with a religious community. There is ample empirical reason to expect protective effects of such involvement. Again, the final decision is always the client's, but encouragement can make a difference. Reengagement with religious traditions

and communities can be an important element of connection with a client's culture of origin, particularly in cultures (e.g., African-American, Native American) where religion is of central and defining importance.

4.4.3. Spiritual Disciplines. A similarly large correlational literature points to an inverse relationship between the practice of meditation and alcohol use/abuse (Alexander, Robinson, & Rainforth, 1994). The practice of transcendental meditation has been secularized by Benson (1973), and its benefits do not appear to require the client to adhere to particular religious beliefs. For those with intact religious affiliation, meditation can be incorporated within the client's own R/S context. Clients can be introduced to the practice of meditation during treatment (Marlatt & Kristeller, 1999).

Little else is yet known from research about the possible benefits of R/S practices and how they might be facilitated during alcohol treatment. There is an indication from the AA literature that it may be vital to introduce clients to and engage them in sampling complementary approaches while they are still in treatment. Within Project MATCH, for example, clients who did not sample AA meetings during their 12 weeks of treatment were highly unlikely to do so during the subsequent 3 years (Tonigan, Connors, & Miller, in press).

Relatively untried as a complementary approach is the involvement of clients in a systematic program of spiritual disciplines derived from a particular religious tradition. Christian-sponsored programs (such as those historically provided by the Salvation Army, Teen Challenge in the U.S., and Blå Kors in Scandinavia) often rely primarily on religious exhortation and conversion intermixed with compassionate care. These longstanding ministries themselves deserve careful study. Religious involvement, however, is not typically intended to be sporadic, but like AA, to involve the person in a disciplined way of life. It could be promising, then, to develop and evaluate systematic complementary R/S programs, to be offered in voluntary conjunction, cooperation, and coordination with alcohol treatment systems. Such programs would more closely approximate the naturalistic R/S involvement that appears to exert protective effects, as described earlier in this chapter.

One such program is offered at the Na'nizhoozhi Center in Gallup, New Mexico, at the border with the Navajo nation. Designed to serve Navajo and other Native Americans, this detoxification and treatment program incorporated motivational interviewing and the community reinforcement approach (Miller, Meyers, & Hiller-Sturmöhfel, 1999). Behind the Center is a ceremonial compound designed for ritual spiritual practices of the Navajo, including a sweat lodge, ceremonial dances, and sings. Clients can be inducted to the spiritual *Hiina 'ah Bits' os* (Eagle Plume) Society. The R/S components of the NCI program are intended to develop traditional Navajo spirituality and reconnect clients with their cultural and religious heritage.

What would comprise such a complementary program developed from the traditional disciplines and practices of other world religions? A program that draws upon Christian mysticism might include regular disciplined prayer

and meditation, periods of silence and aloneness, scriptural study, and spiritual direction (Foster, 1988). The ancient discipline of fasting, often lost in modern Christianity, seems a natural spiritual practice for breaking dependence on consumption and habit. Fasting, also, is reputed to amplify the benefits of prayer and meditation. Such directed spiritual disciplined could be introduced though a focused residential retreat of a week or longer, through day-long sessions, or incorporated into daily life (paralleling residential, intensive outpatient, and outpatient treatment, respectively).

Similar complementary R/S programs could be developed from the disciplines of other world religions such as Judaic, Hindu, Sikh, Muslim, or Buddhist traditions. Opportunity for immersion in Buddhist practices is often available through ashrams or monasteries. Because health professionals often lack in-depth expertise in R/S traditions, there are natural opportunities here for partnership collaborations of treatment programs with local religious leaders, programs, and communities. As with AA, the rationale would not be that of acute treatment—an intense one-time curative experience that begins and ends—but rather one of introducing or reconnecting the person to a disciplined way of living to be continued for a period of years, if not lifelong.

The emphasis in such complementary spiritual components need not and, in many cases, should not be on proselytism or conversion. Their primary usefulness can be in connecting, reconnecting, or deepening the person's ties to his or her own familial and cultural spirituality. There is a certain allure and mystery in exploring unfamiliar religious practices, but I believe that it makes little sense to place Euro-Americans in a sweat lodge, familial Baptists in an ashram, or cultural Jews or Quakers in a charismatic pentecostal meeting as part of their treatment. For those without clear cultural R/S roots or utter alienation from them, an exploration of various spiritual traditions may be valuable, much as one samples a range of AA meetings before settling into a home group.

5. Spirituality and Science

The opportunities are many for enhancing spirituality as a complement to treatment and recovery. Much needed, as these explorations emerge, are well-designed scientific studies of spirituality and alcohol, peer-reviewed, and published through mainstream scientific journals. In exploring spiritual aspects of addiction and recovery, one need not set aside scientific skepticism (Miller, 1998). We owe it to our clients to be open to complementary sources of healing and to evaluate carefully what helps and what does not.

A good head start in this regard was the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 1999 request for applications, which generated 72 proposals and 11 funded projects. The balance to be achieved is between open-mindedness to new possibilities and tough-mindedness through sound, appropriate research methodology. Many pieces of the puzzle of alcoholism are still missing. Measuring treatment approaches, client characteristics, therapist

and treatment processes, and the posttreatment environment, we still account for a minority of the variance in clients' drinking outcomes. It is just possible that in exploring and studying spirituality, we may find some of the missing pieces of the puzzle exactly where, all along, our clients and clinical colleagues have been telling us to look.

References

- Alcoholics Anonymous. (1976). *Alcoholics Anonymous: The Story of How Many Thousands of Men and Women Have Recovered from Alcoholism*, 3rd ed. New York: Alcoholics Anonymous World Services.
- Alexander, C.N., Robinson, P., & Rainforth, M. (1994). Treating and preventing alcohol, nicotine, and drug abuse through transcendental meditation: A review and statistical meta-analysis. In D.F. O'Connell & C.N. Alexander (eds.), *Self-Recovery: Treating Addictions Using Transcendental Meditation and Maharishi Ayur-Veda*. New York: Haworth Press, pp. 13–87.
- Benson, H. (1973). *The Relaxation Response*. New York: William Morrow.
- Brehm, S.S., & Brehm, J.W. (1981). *Psychological Reactance: A Theory of Freedom and Control*. New York: Academic Press.
- Brown, H.P., Jr., & Peterson, J.H., Jr. (1990). Values and recovery from alcoholism through Alcoholics Anonymous. *Counseling and Values* 35, 63–68.
- Deci, E.L. (1985). *Intrinsic Motivation and Self-Determination in Human Behavior*. New York: Plenum Press.
- Fetzer Institute/National Institute on Aging Working Group. (1999). *Multidimensional Measurement of Religiousness/Spirituality for Use in Health Research*. Kalamazoo, Michigan: The Fetzer Institute.
- Foster, R.J. (1988). *Celebration of Discipline: The Path to Spiritual Growth*, 3rd ed. San Francisco: Harper.
- George, L.K., & Ellison, C.G. (2001). Psychosocial mediators of the relationship between religious/spiritual involvement and health: State of the evidence and future directions. Manuscript submitted for publication, Duke University.
- George, L.K., Ellison, C.G., & Larson, D.B. (in press). Explaining the relationships between religious involvement and health. *Psychological Inquiry*.
- Glaser, F.B. (1993). Matchless? Alcoholics Anonymous and the matching hypothesis. In B.S. McCrady & W.R. Miller (eds.), *Research on Alcoholics Anonymous: Opportunities and Alternatives*. New Brunswick, NJ: Rutgers Center on Alcohol Studies, pp. 379–395.
- Gorsuch, R.L., & Miller, W.R. (1999). Measuring spirituality. In W.R. Miller (ed.), *Integrating Spirituality into Treatment: Resources for Practitioners*. Washington, DC: American Psychological Association, pp. 47–64.
- Hazelden Foundation. (1985). You don't have to tear 'em down to build' em up. *Hazelden Professional Update* 4(2), 2.
- Hill, P.C., & Hood, R.W., Jr. (eds.). (1999). *Measures of Religiosity*. Birmingham, AL: Religious Education Press.
- Horstmann, M.J., & Tonigan, J.S. (2000). Faith development in Alcoholics Anonymous: A study of two AA groups. *Alcoholism Treatment Quarterly* 18(4), 75–84.
- Jellinek, E.M. (1952). Phases of alcohol addiction. *Quarterly Journal of Studies on Alcohol* 13, 673–684.
- Keso, L., & Salaspuro, M. (1990). Inpatient treatment of employed alcoholics: A randomized clinical trial on Hazelden-type and traditional treatment. *Alcoholism: Clinical and Experimental Research* 14, 584–589.
- Kurtz, E. (1988). *A.A.: The Story*. San Francisco: Harper & Row.
- Kurtz, E., & Ketcham, K. (1992). *The Spirituality of Imperfection*. New York: Bantam Books.
- Larson, D.B., Swyers, J.P., & McCullough, M.E. (eds.) (1998). *Scientific Research on Spirituality and Health: A Consensus Report*. Rockville, MD: National Institute for Healthcare Research.
- Laundergan, J.C. (1982). *Easy Does It: Alcoholism Treatment Outcomes, Hazelden and the Minnesota Model*. Minneapolis: Hazelden Foundation.

- Marlatt, G.A., & Kristeller, J.L. (1999). Mindfulness and meditation. In W.R. Miller (ed.), *Integrating Spirituality into Treatment*. Washington, DC: American Psychological Association, pp. 67–84.
- May, G.G. (1991). *Addiction and Grace*. San Francisco: Harper.
- Meyers, W.R., & Miller, W.R. (eds.) (2001). *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: Cambridge University Press.
- Meyers, R.J., & Smith, J.E. (1995). *Clinical Guide to Alcohol Treatment: The Community Reinforcement Approach*. New York: Guilford.
- Milam, J.R., & Ketcham, K. (1983). *Under the Influence: A Guide to the Myths and Realities of Alcoholism*. New York: Bantam Books.
- Miller, W.R. (1998). Researching the spiritual dimensions of alcohol and other drug problems. *Addiction* 93, 979–990.
- Miller, W.R., & Bennett, M.E. (1998). Addictions: Alcohol/drug problems. In D.B. Larson, J.P. Swyers, & M.E. McCullough (eds.), *Scientific Research on Spirituality and Health: A Consensus Report*. Rockville, MD: National Institute for Healthcare Research, pp. 68–82.
- Miller, W.R., & C'deBaca, J. (1994). Quantum change: Toward a psychology of transformation. In T. Heatherton & J. Weinberger (eds.), *Can Personality Change?* Washington, DC: American Psychological Association, pp. 253–280.
- Miller, W.R., & C'de Baca, J. (2001). *Quantum Change: When Epiphanies and Sudden Insights Transform Ordinary Lives*. New York: Guilford.
- Miller, W.R., & Hester, R.K. (2003). Treating alcohol problems: Toward an informed eclecticism. In R.K. Hester & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, 3rd ed. Boston, MA: Allyn & Bacon, pp. 1–12.
- Miller, W.R., & Kurtz, E. (1994). Models of alcoholism used in treatment: Contrasting A.A. and other perspectives with which it is often confused. *Journal of Studies on Alcohol* 55, 159–166.
- Miller, W.R., Meyers, R.J., & Hiller-Sturmhofel, S. (1999). The community-reinforcement approach. *Alcohol Health & Research World* 22, 116–121.
- Miller, W.R., Meyers, R.J., Tonigan, J.S., & Grant, K.A. (2001). Community reinforcement and traditional approaches: Findings of a controlled trial. In R.J. Meyers & W.R. Miller (eds.), *A Community Reinforcement Approach to Addiction Treatment*. Cambridge, UK: Cambridge University Press.
- Miller, W.R., & Thoresen, C.E. (2001). Spirituality, religion, and health: An emerging research field. Manuscript submitted for publication.
- Miller, W.R., & Wilbourne, P.L. (2002). Mesa Grande: A methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 97, 265–277.
- Montgomery, H.A., Miller, W.R., & Tonigan, J.S. (1995). Does Alcoholics Anonymous involvement predict treatment outcome? *Journal of Substance Abuse Treatment* 12, 241–246.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA). (1999). *Conference Summary: Studying Spirituality and Alcohol*. Kalamazoo, MI: The Fetzer Institute.
- Nowinski, J., Baker, S., & Carroll, K. (1992). *Twelve Step Facilitation Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence*, Project MATCH Monograph Series, No. 1. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism.
- Ouimette, P.C., Finney, J.W., & Moos, R.H. (1997). Twelve-step and cognitive-behavioral treatment for substance abuse: A comparison of treatment effectiveness. *Journal of Consulting and Clinical Psychology* 65, 230–240.
- Project MATCH Research Group. (1993). Project MATCH: Rationale and methods for a multisite clinical trial matching patients to alcoholism treatment. *Alcoholism: Clinical and Experimental Research* 17, 1130–1145.
- Project MATCH Research Group. (1997). Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. *Journal of Studies on Alcohol* 58, 7–9.
- Project MATCH Research Group. (1998). Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. *Alcoholism: Clinical and Experimental Research* 22, 1300–1311.
- Pruyser, P.W. (1976). *The Minister as Diagnostician: Personal Problems in Pastoral Perspective*. Philadelphia: Westminster John Knox.

- Shavelson, L. (2001). *Hooked: Five Addicts Challenge Our Misguided Drug Rehab System*. New York: New Press.
- Sisson, R.W., & Mallams, J.H. (1981). The use of systematic encouragement and community access procedures to increase attendance at Alcoholics Anonymous and Al-Anon meetings. *American Journal of Drug and Alcohol Abuse*, 8, 371-376.
- Task Force on the Social and Health Effects of Alcohol Use and Abuse. (1986). *Alcohol Use & Abuse: The Social and Health Effects*. New York: The Program Agency, Presbyterian Church (U.S.A.).
- Tonigan, J.S., Ashcroft, F., & Miller, W.R. (1995). A.A. group dynamics and 12-step activity. *Journal of Studies on Alcohol*, 56, 616-621.
- Tonigan, J.S., Connors, G., & Miller, W.R. (in press). Participation and involvement in Alcoholics Anonymous. In T.F. Babor & F.K. DelBoca (eds.), *Treatment Matching in Alcoholism*. Cambridge, UK: Cambridge University Press.
- Tonigan, J.S., Miller, W.R., & Connors, G.J. (2001). The search for meaning in life as a predictor of alcoholism treatment outcome. In R. Longabaugh & P.W. Wirtz (Eds.), Project MATCH hypotheses: Results and causal chain analysis (pp. 154-165). Project MATCH Monograph Series, Vol. 8. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism.
- Tonigan, J.S., & Toscova, R. (1998). Mutual-help groups: Research and clinical implications. In W.R. Miller & N. Heather (eds.), *Treating Addictive Behaviors*. New York: Plenum Press.
- Tonigan, J.S., Toscova, R.T., & Connors, G.J. (1999). Spirituality and the 12-step programs: A guide for clinicians. In W.R. Miller (ed.), *Integrating Spirituality into Treatment*. Washington, DC: American Psychological Association, pp. 111-131.
- Venner, K.L., & Miller, W.R. (2001). Progression of alcohol problems in a Navajo sample. *Journal of Studies on Alcohol* 62, 158-165.
- Waller, N.G., Kojetin, B.A., Bouchard, T.J., Jr., Lykken, D.T., & Tellegen, A. (1990). Genetic and environmental influences on religious interests, attitudes, and values: A study of twins reared apart and together. *Psychological Science* 1, 138-142.
- Yablonsky, L. (1965). *Synanon: The Tunnel Back*. New York: Macmillan.
- Yablonsky, L. (1989). *The Therapeutic Community: A Successful Approach for Treating Substance Abusers*. New York: Gardner Press.

Research Priorities for Alcoholism Treatment

Mary E. McCaul and Peter M. Monti

1. Context for Setting Research Priorities

In November, 1999, the Subcommittee for the Review of the Extramural Research Portfolio for Treatment of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) was convened. The goals of the review process were to assess the breadth, coverage, and balance of the current treatment research portfolio and to identify areas that are either understudied or are potentially key scientific areas that warrant increased attention. The NIAAA sought the Subcommittee's advice and guidance on the scope and direction of extramural treatment research activities.

As cochairs of the Subcommittee, Drs. Mary McCaul and Peter Monti worked with members of the NIAAA Advisory Council (Drs. Marc Galanter and Barbara Mason), an additional alcohol treatment expert (Dr. William Miller), and three individuals with expertise in non-alcohol-related treatment areas (Drs. David Barlow, Stephen Higgins, and Tracie Shea). Experts in a wide variety of alcohol treatment research areas were invited to prepare summaries of current knowledge and prioritize areas for future research efforts.

At the meeting, the experts were asked to recommend two key issues in their specific research areas. The Subcommittee members compiled and edited the recommendations to integrate related issues into broader priority areas. After obtaining further feedback from the assembled experts, the Subcommittee voted on the final priority list to rank the items for perceived opportunities and impact on the field. This process provided considerable breadth of input into the formulation of the priority research areas. Hopefully,

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many researchers across diverse topic areas will find opportunities for new or redirected efforts framed by the proposed priority list.

2. Impact of Prior Portfolio Reviews in Stimulating Research

It is noteworthy that this process is not just an academic review of the current state of the field but that it contributes meaningfully to future research funding and growth. Prior to the 1999 review meeting, the most recent scientific review of the treatment portfolio was conducted more than a decade ago by the Fifth Ad Hoc Extramural Science Advisory Board. The Executive Summary of the resulting report identified six research goals for the coming decade:

- development of reliable classifications of subtypes of alcoholics who can be matched to treatments to maximize effectiveness;
- development of improved treatment outcome measures that are sensitive to changes in biological, social, and psychological functioning;
- identification and clinical evaluation of new pharmacological agents;
- evaluation of the effectiveness of behavioral, psychosocial, and mutual-help approaches through randomized controlled trials;
- determination of cost-benefits and costs offsets of alcoholism treatment through carefully controlled studies; and
- description of treatment systems and service networks.

The remarkable acceleration in the development of medications for alcohol use disorders during the last decade exemplifies the potential impact of this priority-setting process. During the 1990s, the NIAAA Treatment Research Branch funded 48 human pharmacotherapy trials, increasing from an active portfolio of 5 projects in 1990 to more than 26 clinical trials and 9 human laboratory studies in 2000. Progress in medication development is highlighted by the 1994 U.S. Food and Drug Administration's (FDA) approval of naltrexone for alcoholism treatment. This medication is only the second drug approved for alcoholism treatment and the first pharmacotherapy that derives from preclinical and clinical research on the role of neurotransmitters in the development and maintenance of alcohol dependence. Several other medications currently in the pipeline for FDA approval are similarly grounded in the neuroscience of alcohol use and dependence and are examples of the rapid advances in clinical research in this area (see Section IV, Pharmacotherapy).

Similarly, advances in adolescent treatment research crosscut several of the goals of the earlier portfolio review. Most progress has been made in evaluating the effectiveness of treatment approaches through randomized clinical trials. In the past 5 years, approximately 12 clinical trials have been funded under a joint Request for Applications sponsored by the National Institute on Alcohol Abuse and Alcoholism and the Center for Substance Abuse Treatment. These projects are wide in scope and diversity and range from testing the effectiveness of family

therapy for treating alcohol use disorders in adolescents to exploring the benefits of motivational enhancement interventions for alcohol problems among street youth recruited through shelters or adolescents with alcohol-related problems recruited in emergency departments. Two additional areas of adolescent research that have been targeted for emphasis include pretreatment identification and brief intervention and enhancement of posttreatment functioning.

Finally, the spin-off of the NIAAA Health Services Research Program from the Treatment Research Branch highlights the rapid growth in research questions, measurement procedures, and analytic approaches in cost-benefits, cost offsets, and treatment systems and service networks. Such research is already yielding interesting findings of scientific and practical importance. For example, although drinking behavior is correlated with functioning over long periods of time, the magnitude of these correlations varies widely, and the relationship found between drinking and health costs is quite low in some studies. Thus, Stout (this volume) calls for further research on the nature of the relationship between drinking, functioning, and costs over time and on the many variables that may moderate these relationships.

3. New Research Priorities

Using the process described above, five research priorities were identified during the 1999 NIAAA Treatment Research Portfolio Review.

3.1. Mechanisms of Action of Treatment

During the last decade, there has been considerable progress in identifying effective psychosocial and pharmacological treatments for alcoholism. A variety of psychosocial interventions have been manualized and subjected to rigorous evaluation through randomized clinical trials. For example, cognitive-behavioral therapy (CBT), perhaps the most widely studied of the psychosocial interventions, has emerged in recent meta-analyses as either first (Holder et al., 1991) or second (Miller et al., 1995; Finney & Monahan, 1996) among treatments on the basis of effectiveness. Nevertheless, as Kadden points out in this volume, Longabaugh and Morgenstern (1999) recently concluded that despite its strong theoretical foundation and impressive efficacy data, no evidence fully supports its mechanism of action. Longabaugh and Morgenstern aptly express concern that inadequate understanding of mechanisms may impair the ability to replicate treatment successes and may hinder efforts to enhance effectiveness.

For continued progress in treatment development, it is essential to identify and test the theoretical underpinnings of new and ongoing treatments and to develop a better understanding of the biological, psychological, behavioral, social, and environmental mechanisms of these interventions. Examples of such research include elucidating causal chains underpinning treatment effects, testing mediators and moderators of therapeutic processes, determining the

relative contributions of skills training versus motivational enhancement to treatment outcomes, developing more accurate models of treatment and placebo effects, and clarifying the additive and subtractive effects of complex therapies. Development of new or enhancement of existing, theory-based behavioral interventions, including psychotherapies, behavior therapies, cognitive therapies, and family therapies, is needed.

3.2. Combinations and Sequencing of Treatments

Current alcoholism treatments generally have been found to have modest effects. By combining and/or sequencing treatments, it may be possible to enhance outcomes. Research is needed on theory-based therapeutic models of combined treatment or stepped care, particularly focused on tailored interventions for special populations. Combined interventions can include behavioral, cognitive, psychotherapy, support network, or pharmacological treatments.

As with the first priority, understanding the interactive mechanisms of action will be important in designing and testing combined treatments. Treatment analog studies may be useful in this regard because important variables of interest may be more easily controlled in the laboratory than they might be in larger scale studies with a patient population. In addition, combined treatments will require efficacy testing and, at a later stage, studies to determine their suitability for translation. Such studies may test whether a combined treatment shown efficacious in a controlled setting can still be effective when transferred to the community.

A timely example of a combined treatment can be found in NIAAA's Project Combine. In smaller scale pharmacotherapy studies, differential pharmacotherapy effects have been observed as a function of the nature of the combined psychosocial therapy (O'Malley et al., 1992). Project Combine, a multisite, randomized, placebo-controlled clinical trial, will examine the separate and interactive effects of two psychosocial and two pharmacological treatments. In nine study conditions, brief and more intensive motivational and cognitive-behavioral therapies will be studied in combination with naltrexone, acamprosate, or no-medication treatments. Such a project highlights the potential complexity of research design and interpretation in combination studies and also leads the way in propelling clinical trial technology.

3.3. Health-Seeking Patterns and Processes

It is evident that the majority of individuals with alcohol-related problems change their drinking patterns and associated problems without intensive formal treatment intervention, either through natural resolution or brief motivational interventions in health care and other settings.

It is critical to develop a better theory-based understanding of these natural change efforts and health-seeking behaviors. Key areas of research include factors that promote and sustain movement toward recovery, processes of care

engagement (e.g., proactive versus reactive approaches), compliance with care recommendations, retention in change processes, and maintenance of change. As pointed out in the Humphreys chapter (this volume), research is also needed to evaluate the effect of community-based recovery networks (e.g., 12-step groups) on both alcohol-related and psychosocial outcomes. Such work should seek to understand the processes through which change occurs as well as how such networks might effectively interact with professional treatments, including brief interventions (see Fleming chapter). Prospective longitudinal studies should include an analysis of the cost-effectiveness and health care cost offsets of self-help influenced treatments.

3.4. Concurrent Disorders: Medical, Drug, and Psychiatric

Individuals with alcohol use disorders have exceptionally high rates of co-occurring disorders, including medical comorbidity, nicotine and other drug disorders, and psychiatric disorders. As described in the Hurt chapter (this volume), the prevalence of smoking among alcohol-dependent persons is two to three times higher than in the general population, and treated alcohol-dependent persons are at greater risk of death from smoking-related illnesses than from alcohol-related morbidities. Similarly, comorbid psychiatric disorders, particularly depression and anxiety, are elevated among alcohol-dependent individuals compared with the general population, and are generally associated with poorer alcoholism treatment compliance and outcomes (see Cornelius chapter). During the last decade, there has been considerable progress in characterizing the prevalence of these comorbid conditions. However, research is just beginning to address the significant gap in the knowledge that is needed to improve identification, assessment, and treatment of persons with comorbid conditions.

Research is needed to better understand patient characteristics associated with different concurrent disorders (e.g., diagnostic status, biological status, phenotyping, developmental staging), more clearly elucidate the effects of concurrent disorders on alcoholism treatment outcomes and vice versa, understand the process of change in the nonalcohol comorbid disorder, and develop specialized interventions for comorbid patients. In addition, assessment instruments and methods need to be enhanced to measure the broader range of characteristics and outcomes relevant to these populations. Such research will be of considerable scientific and clinical importance and should be a high priority, given the urgent need for improved practice standards in the treatment community.

3.5. Help Agent Behaviors

Although it is well recognized that change processes and outcomes are affected by helping agents (e.g., therapist, health care provider, clergy, family member, concerned significant other), this area of research has received little attention within the alcoholism field. For example, as addressed in the Najavits chapter, clinicians exert considerable influence on retention and outcomes in

alcoholism treatment and often account for more variance in outcome than active treatments or patient characteristics (Najavits and Weiss, 1994). Yet, clinician background characteristics (e.g., experience, training, recovery status) and patient-clinician matching do not adequately explain these powerful clinician effects. Similarly, support networks, both preexisting social networks and networks developed specifically to facilitate recovery, are powerful predictors of relapse and recovery status among treated and untreated alcoholics and problem drinkers (see Longabaugh chapter). However, despite the widespread use of self-help recovery networks, very little empirically validated information is available about the impact of these affiliations on therapeutic outcomes. Finally, although environmental contexts are important determinants of natural resolutions to drinking problems (see Tucker chapter), relatively little is known about the specific contexts and processes that support positive behavioral change.

Theory-driven models for evaluating provider effects are needed. This research could include provider attributes (characteristics, cognitions, beliefs), processes between change agent and client, and training or interventions aimed at the change agent rather than the client. Design innovations (e.g., learning from expert providers) and statistical strategies must be developed to address the methodological problems inherent in this line of research. Research also is needed to explore the change processes through which help agents effect improvement in the alcohol-dependent individual. For example, recent studies have suggested the potential role of enhanced coping and self-efficacy, increased commitment to abstinence and appraisal of substances as harmful, and expanded sober friendship networks as components of the change process associated with AA involvement (Humphreys et al., 1999).

4. Crosscutting Issues

In the course of the Treatment Portfolio Advisory meeting, four issues emerged that, it was felt, crosscut the list of research priorities, that is, rather than representing a priority in themselves, they represented methodological or conceptual issues that need to be considered across priority areas.

4.1. *Special Populations*

Historically, much of alcoholism treatment research has been conducted in the predominant patient population, that is, adult Caucasian men. In recent years, there have been deliberate efforts to expand the pool of study participants to include women; diverse racial, ethnic, and cultural groups; and persons across the life span. These efforts have started to provide evidence for the importance of tailoring treatment to better address the needs of special populations. An obvious example is NIAAA's development of a growing portfolio of adolescent treatment research, described earlier. However, studies in diverse treatment samples have

underscored the need for research on treatments specifically developed for women, older adults, Native Americans, and African-Americans. It remains an important goal in treatment research to enroll sufficient numbers of subjects to permit subanalyses of special populations.

4.2. Patient-Treatment Matching

Project MATCH findings have often been misinterpreted as suggesting that patient-treatment matching has very limited or no utility in improving treatment outcomes. However, a variety of new classification or matching strategies appear to offer promise for future investigation. For example, recent findings (Pettinati et al., 2000) have suggested improved pharmacotherapy effects using the serotonin reuptake inhibitor, sertraline, in Type A alcohol-dependent persons who have a lower risk and severity of alcoholism and lower psychopathology. A current exciting area of research is the use of biomarkers to predict those patients who are most likely to respond to a given intervention. For example, patients who are high in alcohol cue reactivity have been shown to be more responsive to cue exposure treatment (Monti, Rohsenow, & Hutchinson, 2000). Such research highlights the importance of both refining systems for classifying subtypes of alcohol problems and dependence and applying these classifications in study design and data analyses.

4.3. Measurement Techniques

The development of new treatments that often combine multiple components has created a need for complex experimental studies. As Stout points out (see chapter), there have been methodological developments in several areas that, in principle, should allow more effective study implementation and more accurate conclusions, but there are impediments to realizing these goals.

Numerous methodological issues need to be explored such as balancing subject participation demands and study requirements, more fully understanding treatment failure as well as success; using alternative measures of outcome (e.g., event duration measures); understanding the relationships between drinking, functioning, and costs over time, and understanding the basic parameters of follow-up research. Fuller understanding in these areas will improve the replicability of research findings and will also provide information to maximize treatment effectiveness.

In addition to the above issues relating to research design and implementation, advances in data analysis that have significant promise for application to alcohol treatment research need to be technologically transferred to promote better application. Beyond technology transfer, there is a need for technology development in areas where there are well-known methods that simply have not been used in alcohol research. Methods such as formal decision analysis, simulation, and nonlinear modeling represent areas where further development must precede application to the alcohol treatment field.

4.4. Technology Transfer

As described throughout this volume, the treatment research community has made exciting advances, resulting in improved assessment and treatment of alcohol use disorders. However, there have been significant limitations in translating these research advances into practice. First, findings of efficacy in highly controlled research studies do not reliably translate to improved effectiveness in nonresearch settings. It will be critical to future treatment research progress that we develop a better understanding of the factors that contribute to this translational failure. Second, efficacious treatments are not consistently incorporated into practice. Certainly, a variety of issues contribute to this, including failure to adequately disseminate the information in forums and formats that are accessible to the treatment community; a perceived lack of relevance of some treatment research areas with inadequate attention to the practical concerns of clinicians and administrators; concerns about additional cost and staff burden associated with the implementation of new programs and services; and finally, philosophical disagreements between research and treatment staff. Recent examples of this translational failure include the limited adoption of pharmacotherapy using naltrexone and psychosocial treatment based on motivational enhancement therapy. During the next decade, crosscutting goals for treatment outcome research will include developing a research portfolio that is more in tune with the treatment community's need for knowledge in key areas as well as developing more effective strategies for translation and dissemination where knowledge already exists.

5. Mechanisms of Funding

Several mechanisms of funding were discussed at the conclusion of the portfolio review. These can broadly be categorized as National Institutes of Health (NIH) opportunities and all others. Among the NIH mechanisms discussed, Stage 1 psychotherapy development studies that have their underpinnings in basic behavioral sciences should be emphasized. In addition, under the Institute's Health Services Research Portfolio, emphasis should be placed on effectiveness studies. On a somewhat smaller scale, there is a need to promote the availability of career development and conference awards to increase the interests of biostatisticians in alcoholism treatment research. A need was also articulated for funding across NIH institutes for some of the larger scale transinstitute type projects (e.g., comorbidity studies).

Other mechanisms of funding should also be explored. Transagency funding that cuts across agencies such as the Veteran's Administration, the Department of Defense, or the Center for Substance Abuse Treatment might prove profitable. Also, with continued development of the institute's pharmacotherapy program, research support from the pharmaceutical industry should be more aggressively pursued.

6. Summary and Conclusions

The goals of the current NIAAA review process were to assess the breath, coverage, and balance of the treatment research portfolio and to identify areas for increased attention. Both alcoholism treatment experts and non-alcohol-related treatment experts were called upon to help with this task. Our group was encouraged by the fact that results from previous reviews have effectively been incorporated into the institute portfolio, particularly in the areas of the pharmacotherapy and psychotherapy development programs.

The present review identified the five priority areas: mechanisms of action of treatment, combination and sequencing of treatments, health-seeking patterns and processes, concurrent disorders, and understanding help agent behaviors. In addition, several methodological and/or conceptual issues emerged that it was felt, crosscut these areas. These issues included greater emphasis on intervention testing in special populations, patient-treatment matching, measurement techniques, and technology transfer. Finally, several mechanisms of funding were outlined, including across-institute initiatives that could facilitate larger scale translational work such as comorbidity studies and/or studies of combined treatments.

All the above were deemed important by the advisory committee, but an overarching emphasis was placed on understanding the mechanisms of action of treatment. For example, it is important to know that a particular pharmacotherapy reduces craving and also how this comes about. Similarly, it is key to the continued refinement of psychosocial treatments that the active components and their mechanisms of change be clarified. Such mechanism studies are crucial for the development of more heuristic and more accurate theoretical formulations that must guide our understanding of alcohol dependence if treatment, relapse, and recovery are to become more scientifically grounded.

References

- Finney, J.W., & Monahan, S.C. (1996). The cost-effectiveness of treatment for alcoholism: A second approximation. *Journal of Studies on Alcoholism* 29, 229–243.
- Holder, H., Longabaugh, R., Miller, W.R., & Rubonis, A.V. (1991). The cost effectiveness of treatment for alcoholism: A first approximation. *Journal of Studies on Alcohol* 52, 517–540.
- Humphreys, K., Mankowski, E., Moos, R.H., & Finney, J.W. (1999). Do enhanced friendship networks and active coping mediate the effect of self-help groups on substance abuse? *Annals of Behavioral Medicine* 21, 54–60.
- Longabaugh, R., & Morgenstern, J. (1999). Cognitive-behavioral coping-skills therapy for alcohol dependence: Current status and future directions. *Alcohol Research and Health* 23, 78–85.
- Miller, W.R., Brown, J.M., Simpson, T.L., Handmaker, N.S., Bien, T.H., Luckie, L.F., Montgomery, H.A., Hester, R.K., & Tonigan, J.S. (1995). What works? A methodological analysis of the alcohol treatment outcome literature. In R.K. Hester & W.R. Miller (eds.), *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, 2nd ed. New Jersey: Allyn and Bacon, pp. 12–44.
- Monti, P.M., Rohsenow, D.J., & Hutchinson, K.E. (2000). Toward bridging the gap between biological, psychobiological and psychosocial models of alcohol craving. *Addiction* 95, S229–S236.
- Najavits, L.M., & Weiss, R.D. (1994). Variations in therapist effectiveness in the treatment of patients with substance use disorders: An empirical review. *Addiction* 89, 679–688.

- O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry* 49, 894–898.
- Pettinati, H.M., Volpicelli, J.R., Kranzler, H.R., Luck, G., Rukstalis, M.R., & Cnaan, A. (2000). Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcoholism: Clinical & Experimental Research* 24(7), 1041–1049.

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