ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Research Opportunities for Medications to Treat Alcohol Dependence: Addressing Stakeholders' Needs

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During the past decade, significant advances have been made in the development of medications to treat alcohol dependence. Four medications have been approved by the U.S. Food and Drug Administration for treating alcohol dependence—naltrexone, injectable naltrexone, acamprosate, and disulfiram—and several others show promise. The fact remains, however, that because of the heterogeneity of alcohol dependence, these medications will not work for all people, in all circumstances. Moreover, clinicians are not routinely prescribing these medications for alcohol treatment. This commentary poses a number of issues that must be addressed in order to advance the alcohol research field and to make medications a mainstream treatment for problematic drinking. These issues are framed from the perspective of the various stakeholders involved, including clinicians, patients, regulatory agencies, the pharmaceutical industry, and third-party payers. Addressing these issues will not only help to improve treatment but, as further described, will also open up many new research opportunities for alcohol investigators in the coming decade.

Key Words: Alcohol Medication Development, Alcohol Pharmacotherapy, Research Opportunities, Stakeholders' Needs.

DURING THE PAST decade, significant advances have been made in the development of medications to treat alcohol dependence (AD). Four medications have been approved by the U.S. Food and Drug Administration (FDA) for treating AD—naltrexone, injectable naltrexone, acamprosate, and disulfiram—and several others show promise (Johnson, 2008; O'Malley and O'Connor, 2011). The fact remains, however, that because of the heterogeneity of AD, these medications will not work for all people, in all circumstances. Moreover, clinicians are not routinely prescribing these medications for alcohol treatment.

To advance the alcohol research field and to make medications a mainstream treatment for problematic drinking, many issues need to be addressed. Those issues impact a full range of stakeholders, including clinicians, patients, regulatory agencies, the pharmaceutical industry, and third-party payers. Addressing these issues not only will help to improve treatment but also will open up many new research opportunities for alcohol investigators in the coming decade, as described below (see also Table 1).

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WHAT CLINICIANS WANT TO KNOW

First, clinicians want easy-to-use screening materials to assess for hazardous drinking (NIAAA, 2007) and effective alcohol medications (Litten et al., 2012). Consequently, research is needed to elucidate the most efficient avenues for disseminating this information and training clinicians. Once that occurs, the most important decision clinicians face today is determining which medication is the most effective and safe for an individual patient. Advancing personalized medicine allows clinicians to administer medications in a more effective, efficient, and safer manner. Although progress has been made within the alcohol field, particularly in the area of pharmacogenetics (Heilig et al., 2011), much more research is needed.

Once a medication for AD is prescribed, clinicians want to know how long they should administer the medication. Currently, there is little objective information available from research studies. Again, because of the heterogeneity of AD, the duration of treatment may vary with individuals. Also, if a medication is not effective or not well-tolerated by the patient, what is the next step? Would a different medication or a combination of medications, as is done in treating other complex disorders, such as high blood pressure, cancer, and diabetes, be more effective and better tolerated? The biological complexity of AD suggests that a combination of targets is necessary to treat a wider range of patients. Identifying the optimal combination of targets/medications that also produces a tolerable side-effect profile is a high priority over the next decade. Finally, clinicians are interested in learning how to effectively use alcohol medications and behavioral thera-

Table 1. Research Opportunities to Address the Needs of Stakeholders[a]

Clinicians/patients
- Increase awareness of easy-to-use alcohol problem screening instruments and efficacious medications via efficient information dissemination and training programs
- Advance personalized medicine
- Recognize that some patients will require abstinence, whereas others may be able to return to moderate drinking
- Create an algorithm to assist with treatment decisions. Address how long to administer the medication, treatment options if the medication does not work, and strategies for combining medications and combining medications with behavioral therapies
- Develop treatment strategies for AD patients with co-occurring psychiatric, substance abuse, or medical conditions
- Develop strategies to make pharmacological treatments more accessible and affordable to patients

Regulatory agencies
- Develop sensitive endpoint measures that have clear clinical benefit
- Determine the optimal duration period of treatment for alcohol clinical trials

Pharmaceutical industry
- Develop ways to increase the effect size of a tested compound. This includes discovering more efficacious compounds and advancing personalized medicine through increased understanding of the neurological and genetic mechanisms that underlies AD
- Develop and validate screening models that are predictive of clinical success. This includes identifying both animal and human laboratory paradigms
- Improve the methodology of alcohol clinical trials. Areas for refinement include establishing endpoint measures, characterizing the placebo effect and developing strategies to minimize this effect, objectively measuring compliance and alcohol consumption, and developing statistical models based on existing data sets to manage missing data
- Define barriers to medication use and develop effective strategies to offset those obstacles in specialty addiction, primary care, and mental healthcare settings

Third-party payers
- Determine the cost-effectiveness of alcohol medications
- Demonstrate the clinical benefit of primary treatment endpoints

[a]For current program announcements that address these research opportunities, see www.niaaa.nih.gov.

pies together as a treatment option. Specifically, when should behavioral therapy be utilized, before/during/after the administration of medications or in combination with medications? What conditions require specific types of behavioral therapies?

All of these questions create opportunities for future research. One approach is to develop a research algorithm that combines individual patients' demographic characteristics, physiological/biochemical indicators, genome/transcriptome/epigenetic characteristics, cultural indices, and behavioral experiences. Moreover, different components underlying AD exist and must be considered, including reward, negative affect, stress, craving, incentive salience, impulsivity, compulsivity, habituation, executive function, and cognitive function (Litten et al., 2012). Individual vulnerabilities to each of these components also likely exist, adding to the heterogeneity of the disorder. Identifying those variations and integrating them in an algorithm for personalized medicine will be challenging, but fruitful, as we continue to advance our understanding of alcohol seeking and drinking behavior.

Determining an acceptable outcome goal for a patient—either abstinence or low-risk drinking—is another key issue for clinicians. Research shows that some AD patients can successfully reduce their drinking to moderate levels and maintain these levels without risk of relapse or consequences, whereas others must achieve and maintain full abstinence (Dawson et al., 2005). Further research is needed to distinguish between these two types of patients. Recently, Kline-Simon and colleagues (2013) compared abstinent, low-risk, and high-risk drinking groups as a predictor of future drinking and problem outcomes in a large private, nonprofit, integrated healthcare system. Compared with heavy drinkers, low-risk drinkers did as well as abstinent individuals for many of the outcomes important to health and addiction policy, suggesting that low-risk drinking may be an acceptable outcome for some patients undergoing alcohol treatment. Future studies are needed to address this issue in different populations and settings. Last, AD patients generally have a higher prevalence rate of comorbidity than the general population. Thus, in many cases, clinicians encounter AD patients with co-occurring psychiatric, substance abuse, or medical disorders. Many clinical questions remain to be answered. For instance, does the treatment of either the alcohol or comorbid condition improve the outcome of the other? If not, should each disorder be treated independently or in an integrated manner? If an integrated model is the most effective approach, as suggested by recent research (DeVido and Weiss, 2012), should dual disorders be treated concurrently or sequentially? If treated sequentially, in what order? Appropriate treatment strategies may depend on comorbidity types and severities, as well as AD subtypes. Finally, it is important to know if alcohol medications can be prescribed along with other medications used to treat co-occurring medical and psychiatric conditions. It is hoped that future research will develop much needed, evidence-based guidelines for the optimal treatment of these uniquely challenging and understudied populations.

WHAT PATIENTS WANT TO KNOW

What patients want to know about alcohol medications is similar to what clinicians want to know (see above). For instance, patients want to know whether they might have an alcohol problem and what alcohol medications exist. This information is located on the National Institute on Alcohol Abuse and Alcoholism (NIAAA)'s website and in a brochure developed for the public called "Rethinking Drinking" (NIAAA, 2009). Once a problem with alcohol is determined and medication options are explored, patients want to know which medication works best for them. Also, who should the patients see for treatment, a primary care physician, psychiatrist, or an addiction specialist? In addition, what are the barriers that prevent patients from seeking pharmacological treatment for AD? Finally, how affordable are the alcohol medications? Will patients receive reimbursement for the cost of the medications?

WHAT REGULATORY AGENCIES WANT TO KNOW

The FDA's Division of Anesthesia, Analgesia, and Addiction Products current approach to evaluating alcohol medications in clinical trials is to conduct a responder analysis; that is, to a priori define a successful response to medication. Currently, the desired response and primary endpoint of pivotal Phase 3 trials are no heavy drinking (FDA, 2006). This endpoint allows for low levels of drinking and is a significant change from complete abstinence, which previously was the primary endpoint for alcohol pharmacotherapy trials and is currently the only allowable primary endpoint for all other substance abuse trials, including nicotine, opioid, cocaine, and methamphetamine. This change from abstinence to no heavy drinking in alcohol trials was based primarily on studies supported by NIAAA demonstrating a clear clinical benefit associated with no heavy drinking days.

Exploring other treatment endpoints to detect changes in drinking and nondrinking outcomes remains a research need. Those endpoints must show a clinical benefit during the clinical trial, and, ideally, afterward. Clinical benefit can be expressed in many ways, including decreased probability of heavy drinking and dependence, decreased alcohol-related consequences, fewer treatment episodes, and less treatment cost. One approach might be to modify the outcome from no heavy drinking to allow some heavy drinking days (e.g., 1 heavy drinking day per month). Preliminary results indicate that allowing a few heavy drinking days as the endpoint can lead to a significant treatment effect (Falk et al., 2010). First, it must be demonstrated, however, that a few heavy drinking days show the same clinical benefit as no heavy drinking. In addition, guidelines should be established for different levels and patterns of drinking in terms of clinical benefits and risks. These guidelines could be similar to clinical categories developed for blood pressure, cholesterol, and glycated hemoglobin.

Another important objective for the FDA is to determine the optimal treatment duration required to sustain a pattern of nonproblematic drinking for a meaningful period of time. The FDA currently requires 6 months for pivotal trials. Analyses of data sets from alcohol clinical trials are needed to determine whether shorter durations of experimental medications yield information similar to a 6-month trial.

The European Medicines Agency (EMA), the European equivalent to the U.S. FDA, uses different primary endpoints for alcohol clinical trials than the FDA. In addition to complete abstinence as a primary endpoint, the EMA also accepts reduction in alcohol consumption (mg/d) and heavy drinking days (European Medicines Agency, 2010). It is hopeful that the EMA and FDA will, one day, establish similar guidelines for approval of alcohol medications. This would make it easier for pharmaceutical companies to gain approval for promising medications in both European and U.S. markets and further increase their enthusiasm for new central nervous system (CNS) medication development. As described above, research on the relationship between different levels and patterns of drinking versus clinical relevancy would be positive step in developing similar guidelines.

WHAT THE PHARMACEUTICAL INDUSTRY WANTS TO KNOW

Pharmaceutical companies will pursue drug development for a specific medical disorder if (i) there is an unmet need in the treatment community; (ii) the requirements to get experimental medications approved by the regulatory agencies are not too difficult; and (iii) once approved, the public will use the medication. Currently, there are 18 million Americans who are diagnosed with alcohol use disorders and another 40 million who are high-risk drinkers without the diagnosis of alcohol use disorders (Grant and Dawson, 2006). So clearly, there is an unmet need to address the issue of problematic, addictive drinking. However, steering a medication through the existing maze of regulatory agency requirements is challenging, especially because the alcohol medications currently under investigation often have small effect sizes. One solution to this problem is to improve the effect size of tested medications; for example, by focusing on the discovery of more effective targets and advancing the idea of personalized medicine. The ability to identify subjects who are more likely to benefit from an effective experimental medication can be incentive for the pharmaceutical industry to invest in pivotal clinical trials. This stage of drug development is the most expensive part of drug development and also is often unsuccessful (Paul et al., 2010). Only 46% of new compounds targeted to the CNS succeed in pivotal clinical trials (Kaitin and Milne, 2011).

In the drug development process, especially for CNS-targeted medications, a major barrier has been the inability to develop screening models that can be used to predict clinical success (Litten et al., 2012). In the alcohol field, we have excellent animal and human laboratory paradigms that could serve as models. The next step is to establish the predictive value of those models. For example, medications from existing clinical trials (both positive and negative results) could be tested retroactively using a screening model to determine whether that model would have had predictive utility if used prior to the clinical trial. Research also can help to select and validate the most appropriate animal and human laboratory paradigms to use as potential screening models. Ideally, a series of models would be selected to yield a distinct pattern of outcomes for each tested compound. Such a pattern of outcomes would provide valuable information for pharmaceutical companies and aid in making the "Go/No Go" decision of conducting additional time-consuming, expensive clinical trials.

Further refining of the methodology used in alcohol clinical trials may also lead to improvements in the drug development process. Areas that require investigation include establishing realistic primary endpoint measures, overcoming

the placebo effect, accurately measuring compliance and drinking, and managing missing data.

Defining a primary endpoint is important not only to the FDA, but also to the pharmaceutical industry. If the endpoint is too difficult to achieve, companies will be reluctant to pursue the development of medications for alcoholism. The endpoint must be sensitive to the effect of the experimental medication and, most importantly, clinically meaningful.

Another issue that must be addressed pertaining to clinical trials is the placebo effect; a complex, psychobiological event that can mask the effect of the investigational medication. Although the placebo response occurs in all alcohol clinical trials, little is known about its impact on the observed effect size. Research is needed to further characterize and develop strategies to control the placebo response.

Accurately measuring alcohol consumption is essential given that the primary endpoint is based on alcohol consumption. Currently, drinking typically is measured by self-report, primarily by the Timeline Follow-Back method. Research to develop devices that could measure alcohol consumption objectively and in real time would significantly strengthen clinical trial methodology. Some progress has been made in developing alcohol sensors. For instance, the Secure Continuous Remote Alcohol Monitor (SCRAM), although only semi-quantitative in measuring alcohol intake, is being used now in criminal justice settings (Litten et al., 2010). Inventions are needed to develop devices that are more quantitative, less intrusive, and more cost-efficient.

To evaluate the effectiveness of a test medication during a clinical trial, subjects must take the medication as prescribed and remain in the study for the full duration. Methods to accurately measure and improve medication compliance are critical to determine that medication's effectiveness. Noncompliance can lead to an incorrect interpretation of the clinical trial results and a reduction of statistical power (Boudes, 1998; Czobor and Skolnick, 2011). For example, in alcohol trials, medication compliance typically is measured by patient self-report and/or by counting unused pills. The ability to objectively measure the ingestion of a test tablet in real time is one example that could benefit from additional research.

Retaining subjects for the full duration of the trial offers another area for improvement. Missing data resulting from subject dropout make it difficult to estimate the true effect of the medication. Developing a way to approximate outcome values from "dropouts" would help. For example, new statistical models could be developed using data from existing alcohol clinical trials to estimate the values for subjects who drop out of a trial. To enhance these types of analyses, NIAAA has made publically available the COMBINE data (www.niaaa.nih.gov). So far, NIAAA has issued this data set to more than 30 research groups worldwide. NIAAA is planning to release additional data sets from recent multisite alcohol clinical trials.

Finally, once the medication obtains FDA approval, it needs to be adopted by the treatment community and, from the pharmaceutical company's perspective, it must be profitable. For example, it is now estimated that it costs pharmaceutical companies 1.5 billion dollars to develop a compound from discovery to market launch (Levine, 2012) and requires approximately 18 years for CNS medications (Kaitin and Milne, 2011). Thus, there is concern among pharmaceutical companies about the huge cost in developing medications and bringing it to market and whether there will be enough income to recoup their investment. With regard to alcohol medications, the four medications approved by the FDA are not widely prescribed. For example, in 2010, only 658,000 prescriptions for alcohol medications to treat alcohol problems were written in the United States—representing a sales volume of $77 million (IMS Health, 2010). This number is much lower than expected, given the number of Americans with alcohol use disorders. To put this in perspective, the antidepressant Lexapro® had a sales volume of $1.7 billion in 2004 (~ $1.6 billion more than medications for treating alcohol use disorders) even though the number of U.S. adults suffering from major depression is similar to those suffering from alcohol use disorders (Mark et al., 2009). Many reasons exist for the lackluster prescriber acceptance of alcohol medications, including weak marketing efforts, lack of awareness, lack of patient demand, perceived lack of efficacy, patients' refusal to take an alcohol medication, high cost, side effects, shortage of physicians in addiction treatment settings, and lack of organizational support in promoting medications for alcohol treatment (Knudsen et al., 2011; Mark et al., 2003a,b; Oliva et al., 2011; Thomas et al., 2003, 2008). Prescribing barriers must be addressed and effective strategies developed to offset these obstacles to treatment.

Interestingly, most people with alcohol problems do not seek care in a specialty treatment setting. However, many people seek treatment from primary care physicians, not for their alcohol problem, but often for the physical problems it is causing. Thus, research on alcohol medication use should involve general medical settings in addition to addiction specialty settings.

WHAT THIRD-PARTY PAYERS WANT TO KNOW

A vital issue for third-party payers is the cost-effectiveness of the medication. Few studies exist that explore the investment of medication coverage in terms of cost and improvement in outcome. For example, Zarkin and colleagues (2008) demonstrated in the COMBINE trial an increase in the cost-effectiveness of a combination of medical management (MM) therapy and naltrexone as well as a combination of MM, naltrexone, and acamprosate. Likewise, Poldrugo and colleagues (2005) reported from 5 clinical trials that treatment with acamprosate reduced total costs of treatment, particularly the cost of hospitalization. The implementation of the Mental Health Parity and Addiction Equity Act and Affordable Care Act should lead to more comprehensive

coverage, but how that coverage will be applied is unknown. For example, there are a host of policies that restrict coverage, such as the need for prior authorization. Demonstrating cost-effectiveness of a medication will, most likely, help in lifting these restrictions.

The primary endpoints described in the package insert also need to demonstrate a clinical benefit to the third-party payers. For example, the endpoint "total abstinence" is an obvious benefit. However, now that the FDA will accept the primary endpoint of no heavy drinking, insurance companies and other third-party payers must understand the clinical benefit of this endpoint. Research can address this need as well as other clinical endpoints that may be used to describe an outcome.

Improving the integration of treatment services is a major element in healthcare reform. Medication-assisted treatment will be an important part of this. Research opportunities exist to demonstrate the benefits of medications in alcohol treatment. Moreover, strategies need to be developed to integrate this therapy into mainstream medical treatment. These efforts will provide third-party payers with the information they need to support and substantially cover the use of alcohol medications in the treatment of alcohol addiction.

FINAL REMARKS

Significant progress has been made in medications development to treat alcohol addiction, and we are reaching a tipping point in terms of gaining patients' and clinicians' acceptance of those medications in mainstream medicine. Still much work remains. Research is needed to address the many issues and concerns of the various stakeholders. Such research will lead to the discovery and development of efficacious medications, advance the use of personalized medication, and determine effective strategies to integrate medication use for alcohol addiction into mainstream medicine. As we successfully carry out these opportunities, this will, undoubtedly, improve treatment outcomes, a goal that we all share and are working hard to achieve.

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The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of the sponsoring agency or the Federal government.

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