

accompanied by a constellation of depressive symptoms such as changes in eating or sleeping patterns, fatigue, difficulty concentrating, indecision, thoughts of death or suicide, or feelings of worthlessness, helplessness, or hopelessness (16). It is important to note that these symptoms must represent a change from the individual's usual self and cause clinically significant distress or impairment. In addition, they cannot be attributable to bereavement or another disorder, including a substance-induced condition or a general medical condition. In some individuals, hallucinations or delusions may occur in the context of a major depressive episode, in which case the episode would be specified as "Severe With Psychotic Features." When psychotic features are present, they may either be mood congruent (typically involving themes such as guilt, punishment, personal inadequacy, or disease) or mood incongruent. Although not a part of the DSM-IV-TR criteria, anxiety and somatic symptoms (particularly muscular, respiratory, and genitourinary) can also be seen in the context of major depressive disorder (975). Episodes of major depression may also be distinguishable by their longitudinal course (e.g., chronic if symptoms are present for at least 2 years, postpartum onset if symptoms occur within 4 weeks postpartum, seasonal pattern if the timing of episodes is regularly associated with a specific time of year) (16) and characteristic subsets of episode features (Table 12).

## B. EPIDEMIOLOGY

Information on the current prevalence of major depressive disorder comes from two large community surveys, the National Comorbidity Survey Replication (NCS-R) study (976) and the National Epidemiologic Survey of Alcoholism and Related Conditions (NESARC) (655). In the NCS-R, the lifetime prevalence of major depressive disorder among the 9,090 adult participants was 16.2%, with a 12-month prevalence of 6.6%. The NESARC, which included more than 43,000 adults found slightly lower prevalence rates than the NCS-R (13.25% lifetime and 5.28% 12-month), perhaps because the sample included previously omitted groups of individuals with lower prevalence rates (655). A number of sociodemographic factors appears to be associated with an increased prevalence of major depressive disorder, including female sex, being middle-aged, being never or previously married, having a low income, being unemployed, or being disabled (655, 976). In the NESARC, being Native American increased risk relative to being Caucasian, whereas being Asian, Hispanic, or black decreased risk (655).

The impact of major depressive disorders on individuals and their families is substantial. Virtually all individuals in the NCS-R who had a major depressive episode in the

preceding 12-month period experienced significant levels of symptom severity as assessed by an independent rating scale (976). For more than 50% of individuals, symptoms were rated at severe or very severe (976) and were associated with substantial role impairment (977).

Major depressive disorder rarely occurs in isolation; anxiety disorders, substance use disorders, personality disorders, and impulse control disorders commonly co-occur with major depressive disorder in community samples (655, 976) as well as in individuals in psychiatric treatment (978). In the NCS-R, major depressive disorder was found to co-occur with at least one other DSM-IV disorder in two-thirds of those surveyed (976), but from a temporal standpoint major depressive disorder was the primary diagnosis in only about 12% of these individuals (976). In contrast, in a study of patients in psychiatric treatment in the United States, 84% of major depressive disorder patients had at least one co-occurring condition: 61% had a co-occurring Axis I condition, 30% a co-occurring Axis II condition, and 58% a co-occurring Axis III condition (978). Anxiety disorders were the most common co-occurring disorder in the prior 12 months in both the NCS-R (57.5% of the sample) (976) and the NESARC (36.1% of the sample) (655). Of the anxiety disorders, the greatest association was seen with generalized anxiety disorder and the weakest association with specific phobia (655). Substance use disorders in the preceding 12-month period were less common in the NCS-R (8.5%) (976) than in the NESARC, in which 14.1% of the individuals with major depressive disorder had an alcohol use disorder, 26.0% had nicotine dependence, and 4.6% had another substance use disorder (655). Personality disorders were present in 37.9% of individuals with major depressive disorder in the NESARC (655). Obsessive-compulsive, paranoid, schizoid, and avoidant personality disorders were most common among subjects with major depressive disorder; avoidant, dependent, paranoid, and schizoid personality disorders had greater odds ratios for association with major depressive disorder than other personality disorders (655).

Treatment of major depressive disorder does not always occur and may be delayed. The average time to treatment in the NESARC was approximately 3 years, and only about 60% of the sample with major depressive disorder received treatment (655). The NCS-R also evaluated history and adequacy of treatment for major depressive disorder (976). Of respondents who reported having had a major depressive episode in the last year, just more than one-half had received treatment but less than one-half of these individuals (about one-fifth of the total) received adequate treatment (976). These findings highlight the need for changes in the delivery of mental health services to enhance the timeliness and quality of care for major depressive disorder.

**TABLE 11.** DSM-IV-TR Criteria for Major Depressive Episode and Major Depressive Disorder

Diagnosis	Criterion/Symptom Description
Major depressive episode	<p>A. At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (do not include symptoms that are clearly due to general medical condition or mood-incongruent delusions or hallucinations).</p> <ol style="list-style-type: none"> <li>1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)</li> <li>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)</li> <li>3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day</li> <li>4. Insomnia or hypersomnia nearly every day</li> <li>5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)</li> <li>6. Fatigue or loss of energy nearly every day</li> <li>7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)</li> <li>8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)</li> <li>9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide</li> </ol> <p>B. The symptoms do not meet criteria for a mixed episode.</p> <p>C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</p> <p>D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).</p> <p>E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.</p>
Major depressive disorder, single episode	<p>A. Presence of a single major depressive episode.</p> <p>B. The major depressive episode is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.</p> <p>C. There has never been a manic episode, a mixed episode, or a hypomanic episode.</p>

(continued)

**TABLE 11.** DSM-IV-TR Criteria for Major Depressive Episode and Major Depressive Disorder (*continued*)

Diagnosis	Criterion/Symptom Description
Major depressive disorder, recurrent	<p>A. Presence of two or more major depressive episodes (each separated by at least 2 months in which criteria are not met for a major depressive episode).</p> <p>B. The major depressive episodes are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.</p> <p>C. There has never been a manic episode, a mixed episode, or a hypomanic episode</p>

Source. Reprinted from *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*. Washington, DC, American Psychiatric Association, 2000. Copyright © 2000, American Psychiatric Association.

**TABLE 12.** Selected DSM-IV-TR Major Depressive Episode Specifiers

#### Criteria for Melancholic Features Specifier

- A. Either of the following, occurring during the most severe period of the current episode:
  - 1. loss of pleasure in all, or almost all, activities
  - 2. lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)
- B. Three (or more) of the following:
  - 1. distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
  - 2. depression regularly worse in the morning
  - 3. early morning awakening (at least 2 hours before usual time of awakening)
  - 4. marked psychomotor retardation or agitation
  - 5. significant anorexia or weight loss
  - 6. excessive or inappropriate guilt

#### Criteria for Atypical Features Specifier

- A. Mood reactivity (i.e., mood brightens in response to actual or potential positive events)
- B. Two (or more) of the following features:
  - 1. significant weight gain or increase in appetite
  - 2. hypersomnia
  - 3. leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
  - 4. long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment
- C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode.

#### Criteria for Catatonic Features Specifier

The clinical picture is dominated by at least two of the following:

1. motoric immobility as evidenced by catataxis (including waxy flexibility) or stupor
2. excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
3. extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism
4. peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing
5. echolalia or echopraxia

## C. NATURAL HISTORY AND COURSE

The age at onset of major depressive disorder varies widely, although the average age at onset is the late 20s. Although the onset of the first episode is rarely before puberty, the disorder may begin at any age (655, 976). Symptoms of major depressive disorder typically develop over days to weeks. Prodromal symptoms, including generalized anxiety, panic attacks, phobias, or depressive symptoms that do not meet the diagnostic threshold may occur over the preceding several months. In some individuals, however, major depressive disorder may develop suddenly, as in the wake of severe psychosocial stress. The duration of a major depressive episode also varies. The mean duration of a major depressive episode was 16 weeks in the NCS-R (976), with a median duration for the longest depressive episode of 24.3 weeks in the NESARC (655). In treated patients, the median time to recovery from a major depressive episode is approximately 20 weeks (979). Untreated, episodes typically last 6 months or longer. Some patients with major depressive disorder eventually have a manic or hypomanic episode, and they will then receive a new diagnosis of bipolar I disorder or bipolar II disorder.

### 1. Recurrence

Major depressive disorder is unremitting in 15% of patients and recurrent in 35%. About half of those with a first-onset episode recover and have no further episodes (502). After three episodes, the risk of recurrence approaches 100% in the absence of prophylactic treatment. Individuals with major depressive disorder superimposed on dysthymic disorder carry a greater risk for having recurrent episodes of major depressive disorder than those without dysthymic disorder (410). When major depressive disorder is recurrent, its course varies. Some people have episodes separated by many years of normal functioning, others have clusters of episodes, and still others have increasingly frequent episodes as they age.

### 2. Interepisode status

Functioning usually returns to the premorbid level between

episodes. However, 20%–35% of patients have persistent residual symptoms and social or occupational impairment. Patients who continue to have depressive symptoms but fall below the diagnostic threshold for major depressive disorder are considered to be in partial remission. Residual depressive symptoms increase the risk of relapse. Anxiety and somatic symptoms are particularly prominent residual symptoms of major depressive disorder (980).

### 3. Complications and prognosis

Major depressive disorder adversely affects the patient and others. The most serious complication of a major depressive episode is suicide (including suicide/homicide). Major depressive disorder is also associated with significant medical comorbidity and complicates recovery from other medical illnesses, such as myocardial infarction (see Section III.C.1). Beyond its impact on the patient alone, major depressive disorder also affects the patient's marital, parental, social, and vocational functioning (981). The disorder, especially when recurrent or chronic, may distress other individuals in the patient's social network, e.g., children, spouse, and significant others. If the patient is a parent, the disorder may affect his or her ability to fulfill parental role expectations (982) and increase the likelihood of children becoming depressed as well (see Section III.B.5). Major depressive episodes are associated with occupational dysfunction, including unemployment, absenteeism, and decreased work productivity (977, 983). In fact, in terms of the level of disability for the population as a whole, major depressive disorder was second only to chronic back and neck pain in disability days per year (977).

The prognosis for major depressive disorder depends on many factors, such as treatment status, availability of supports, chronicity of symptoms, and the presence of co-occurring medical and psychiatric conditions. With treatment, however, the prognosis is generally good (984). Most patients will respond to acute treatment, and continuation and maintenance treatment with acutely active treatments has been shown to lower the risk and severity of relapse.

## V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

Translating the product of science into a decision about a single human patient raises the concept of epistemology: how we know what we think we know and how certain we can be about that knowledge. Like all guidelines, this one is an attempt to distill clinical research into recommendations that will be clinically applicable to the unique indi-

vidual who presents for treatment. Science can never provide all of the answers that a doctor or patient wishes and, at times, the knowledge base may consist primarily of accumulated wisdom from clinical experience. In addition, every scientific protocol reflects a series of compromises, and each compromise may restrict internal and/or

external validity, as described later in this section. No one study, with its inevitable limits, can reveal “truth.” The wise scientist—and physician—demands replication. When multiple trials, with different methods, come to similar conclusions, the clinician can be reasonably confident in the results.

Many aspects of the design of research studies can influence the interpretation of the data and their implication for clinical practice. When translating efficacy evidence to clinical practice, it is important to assess the adequacy of the sample size (given modest effect sizes of antidepressant treatments), the nature and validity of the control condition, the length of the treatment trial, the nature of the participant population, the type and reliability of the outcome measure, and publication bias (in favor of positive trials) (74, 985, 986).

Some issues also exist that are specific to pharmacotherapy trials. First, it is important to consider whether and what type of comparison group was used (e.g., placebo or active agent). In trials of antidepressant medication treatments, high placebo response rates could make detection of true treatment effects difficult in well-controlled trials, as well as explain observed treatment effects in trials with less robust controls. It is also important to consider whether trials were blinded and, if so, whether medication side effects could reveal the identity of active agents. Issues related to the outcomes measured in trials are important as well. A variety of different outcome measures are employed, and a report of “efficacy” could refer to symptom reduction (e.g., reduction in the frequency or severity of major depressive disorder symptoms), response (e.g., reduction in major depressive disorder symptoms below a threshold), or prevention of relapse. Despite the fact that a 2006 American College of Neuropsychopharmacology task force report (408) emphasized the need to aim for remission as a primary goal, studies may not be designed and powered statistically to assess remission as a primary outcome. Until recently most research studies have reported response rates, often defined as a reduction by 50% in the measured severity of depression. In addition, data often come from short-term (6- to 12-week) efficacy trials that cannot show whether treatments are effective over the medium- and long-term. There has also been recent concern that the apparent effect size of antidepressants has been exaggerated, due to the lack of reporting or selective publication of negative clinical trial data (74, 75). A national database of clinical trial data (<http://clinicaltrials.gov/>) is being expanded in an effort to make these data available and transparent (987). However, most meta-analyses were published prior to this initiative, and previously conducted studies will not be subject to the provisions of recent regulations (988).

Evaluating the efficacy of psychotherapeutic approaches for major depressive disorder can also be challenging. Although there have been a number of well-designed trials of CBT and IPT in large samples, for some other types of psychotherapy, few or no clinical trials have been conducted. In studies evaluating psychotherapy against a variety of control conditions such as waiting lists, other forms of psychotherapy, medications, placebos, or a no-control group, it is difficult to make comparisons of the observed treatment effect sizes among trials. Some trials have not examined the effects of psychotherapy exclusively among patients with major depressive disorder and may not have specifically assessed improvement in major depressive disorder as an outcome. In other trials, the nature of the psychotherapeutic intervention has been insufficiently described, making it difficult to apply the study findings to psychotherapeutic approaches used in practice.

In evaluating the impact of a particular intervention, several statistical concepts are helpful to understand. If one starts with the assumption that the treatment group and the control group are equivalent (i.e., no effect of treatment), the *p* value indicates the probability that the treatment group will show an outcome that is equal to or more extreme than the observed treatment outcome (989). Although specific values of *p* (e.g., 0.05) are commonly considered to be statistically significant, the *p* value does not address the possibility, known as a type II error, that the treatment group and control group will have similar outcomes even though the treatment is actually effective. This possibility can be reduced, to some extent, by using sufficiently sized research samples, which should be calculated as part of the study design (i.e., power analysis). Because these concepts are difficult to grasp and provide limited information about the clinical importance of an observed impact of treatment, several other measures are often used. One approach to indicating the benefit of a treatment relative to a control condition is the number needed to treat (NNT), which is the number of individuals who would have to be treated to prevent one negative outcome (or benefit one patient) (990). When applied to adverse effects, such a measure is termed the number needed to harm (NNH). The effect size is a measure of the magnitude of the difference between the treatment group and the control group, which also considers the variability of the measurements. When the statistic Cohen’s *d* is used to measure the size of a treatment effect, a general rule-of-thumb is that *d*=0.2 represents a small effect, *d*=0.5 represents a medium effect, and *d*=0.8 (or greater) represents a large effect of the intervention (991). In addition to being used in describing the results of individual studies, effect sizes are also used in comparing and synthesizing the results of multiple clinical trials through meta-analyses.

## A. ACUTE PHASE SOMATIC TREATMENTS

### 1. Antidepressant medications

#### a. Selective serotonin reuptake inhibitors

Many studies and meta-analyses have compared SSRIs among themselves as well as with other classes of antidepressants. Differences in efficacy and tolerability between SSRIs and TCAs, assessed through a meta-analysis of 102 studies (85), found no overall difference in efficacy between TCAs and SSRIs. However, TCAs appeared more efficacious in inpatients ( $p=0.012$ ), and amitriptyline was more effective than SSRI comparators ( $p=0.012$ ), although publication bias could not be excluded. By contrast, SSRIs as a class ( $p<0.01$ ) and, more specifically, paroxetine ( $p=0.001$ ), fluoxetine ( $p<0.01$ ), sertraline ( $p<0.05$ ), and citalopram ( $p<0.01$ ) had a significantly lower rate of dropouts for side effects. Other meta-analyses have compared the SSRIs among themselves and with other newer antidepressant agents. Cipriani and colleagues (96) performed a multiple-treatments meta-analysis, which encompassed 117 randomized controlled trials and 25,928 subjects. Incorporating efficacy and treatment discontinuation, they found the greatest degree of overall acceptability with escitalopram and sertraline, with greatest efficacy for mirtazapine, escitalopram, venlafaxine, and sertraline as compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Gartlehner and colleagues (95) also compared the benefits and side effects of second-generation antidepressants including SSRIs using 6 good- or fair-quality systematic reviews or meta-analyses and 155 good- or fair-quality double-blind, placebo-controlled, or head-to-head randomized controlled trials of at least 6 weeks' duration to assess efficacy and 35 observational studies with at least 100 participants and follow-up of at least 12 weeks to assess harms. Although the side effect profiles and onset of action differed among the antidepressants, no differences in efficacy or effectiveness were found.

A systematic review of 28 randomized studies (89) showed that, even in anxious depression, SSRIs (fluoxetine, paroxetine, citalopram, sertraline, and escitalopram) are comparable in efficacy to other antidepressant medications (bupropion, amitriptyline, mirtazapine, imipramine, nefazodone, and venlafaxine), both in depression and anxiety parameters. When compared with venlafaxine, fluoxetine was less effective both in depression and anxiety scores, while paroxetine was less effective in anxiety scores only. No differences were found between venlafaxine and the other SSRIs.

A Cochrane meta-analysis (84) that included 132 randomized studies (almost all double blind) did not find sig-

nificant differences in fluoxetine efficacy versus TCAs. When fluoxetine was compared with newer antidepressants, venlafaxine was superior, and within the class of SSRIs, sertraline was significantly superior. However, fluoxetine was significantly better tolerated than TCAs as a class and, more specifically, was better tolerated than amitriptyline, clomipramine, desipramine, and imipramine; no differences were noted in comparison with all of the other medications. Similar meta-analyses compared sertraline (126) and escitalopram (992) to other antidepressive agents. Although differences were small, there was a trend for sertraline to be more acceptable and efficacious than comparator antidepressants, including TCAs, SSRIs, and several newer antidepressants (126). Escitalopram was found to be more efficacious than citalopram and fluoxetine in terms of response and remission of depressive symptoms and was associated with lower rates of treatment discontinuation than subjects receiving duloxetine (992).

Another meta-analysis of 21 studies (98) compared efficacy and tolerability of each SSRI (except escitalopram) against the SSRI class overall and showed no difference in efficacy among the drugs. Rates of dropout due to side effects were significantly lower in patients treated with sertraline ( $p<0.05$ ) and significantly higher in patients treated with fluvoxamine ( $p<0.01$ ), although the dropout rate in fluvoxamine-treated patients appeared to vary with medication dose. In this meta-analysis, side effects and discontinuation reactions were observed more often with paroxetine than with other SSRIs. Interaction with other drugs was higher with fluoxetine, fluvoxamine, and paroxetine than with sertraline and citalopram, although citalopram was overrepresented in deaths due to overdose.

A systematic review based on 18 randomized, double-blind trials (94), which compared escitalopram with either citalopram, venlafaxine, paroxetine, sertraline, or bupropion, found no differences in efficacy between escitalopram and the other medications (except for the comparison with citalopram, which showed a significant difference in two of four studies). Rates of study withdrawal due to side effects were lower with escitalopram than with venlafaxine ( $p<0.05$ ) or paroxetine ( $p<0.05$ ).

Another meta-analysis of 32 randomized clinical trials studied the efficacy and tolerability of antidepressants in people older than age 55 years (704). This study found that there was no difference in efficacy between TCAs and SSRIs, but SSRIs were better tolerated. Compared with patients who were taking TCAs, patients who were taking SSRIs were less likely to withdraw from the study overall or because of side effects, in particular. The qualitative analysis of side effects showed a small increase in gastrointestinal and neuropsychiatric side effects associated with TCAs.

Overall, the findings of multiple randomized trials and meta-analyses indicate comparable efficacies for SSRIs relative to TCAs, although some data suggest greater efficacy for TCAs in inpatient samples. Selective serotonin reuptake inhibitors also appear to have comparable efficacy to other non-TCA antidepressants, although venlafaxine shows superior efficacy in some studies, and comparisons of SSRIs and MAOIs have not been done. In terms of tolerability, SSRIs show consistently fewer dropouts in clinical trials than TCAs, and side effects are also reported less often with SSRIs. There also do not seem to be significant differences in efficacy among the SSRIs. Fluvoxamine appears to have more side effects and more problems with drug interactions than the other SSRIs; drug interactions are also more problematic with fluoxetine and paroxetine than with citalopram, escitalopram, or sertraline.

### **b. Serotonin norepinephrine reuptake inhibitors**

The efficacy of venlafaxine, desvenlafaxine, and duloxetine, which are classified as SNRIs, and mirtazapine, which (although not an SNRI) also enhances both serotonin and norepinephrine neurotransmission, has been demonstrated in placebo-controlled studies of depressed patients (101, 102, 105, 113, 993, 994, 995). A number of studies have contrasted these “dual-action” antidepressants with the SSRIs. Although most individual studies have not found statistically significant differences (see, for example, references 226 and 421), meta-analyses of controlled studies of venlafaxine (101, 104, 996, 997), duloxetine (102), and mirtazapine (113) using SSRIs as comparators have generally documented small (i.e., 4%–10%) albeit reliable differences in the likelihood of response or remission favoring the dual-action drugs. Papakostas et al. (995) similarly found an average difference of 4% in response/remission rates in a meta-analysis of a broader grouping of antidepressant drugs that affect norepinephrine and serotonin. These average effects are generally below the magnitude of difference that is widely considered to be clinically significant. It is possible that a small average difference in an overall pool of patients may obscure larger and more meaningful differences among selected subgroups of depressed patients (e.g., more severely depressed patients [102], inpatients [561], or postmenopausal women [998]), but this suggestion has yet to be confirmed by analyses of larger data sets. At present, the efficacy of desvenlafaxine has only been established versus placebo (993, 994); there are not yet any published studies assessing its benefits relative to other antidepressants. Nevertheless, as the principal active metabolite of venlafaxine, it is likely to have a comparable efficacy profile.

Perahia et al. (999) conducted a randomized controlled trial of duloxetine versus paroxetine and placebo in an outpatient setting in patients who met the criteria for major depressive disorder. After 8 weeks, duloxetine at 80 mg/day (N=93) and at 120 mg/day (N=103) was found to be superior to placebo (N=99). However, paroxetine was not superior to placebo in this study. Perahia et al. also conducted a relapse prevention study (1000), in which patients were randomly assigned to receive duloxetine or placebo for 26 weeks after a 12-week open-label treatment phase. The 136 patients who received duloxetine had a relapse rate of 23%, compared with the 39% relapse rate among the 142 patients who received placebo ( $p \leq 0.005$ ). A large cohort study by Raskin et al. (1001) followed 1,279 patients in 52 treatment centers taking 80–120 mg/day of duloxetine over 52 weeks. Patients were assessed by multiple instruments at 6, 28, and 52 weeks. At 6 weeks, 50.8% achieved a score of <8 on the HAM-D. The rate of response increased to 75.6% at week 28 and 81.7% at week 52, with no safety concerns identified in the course of the study.

Venlafaxine extended release (XR) has also been extensively studied. Rudolph and Feiger (1002) conducted an 8-week outpatient trial of venlafaxine XR compared with fluoxetine and placebo. In this trial, 100 patients received venlafaxine XR (75–225 mg/day), 193 received fluoxetine (20–60 mg/day), and 98 received placebo. Remission rates, determined by an HRSD score of <8, were 37% in the venlafaxine XR arm, 22% in the fluoxetine arm, and 18% in the placebo arm. Sauer et al. (1003) compared 76 patients who received venlafaxine XR (75–150 mg/day) with 75 patients who received amitriptyline (75–150 mg/day). Venlafaxine XR yielded response rates of 39.5%, compared with 41.7% for amitriptyline. Saiz-Ruiz et al. (1004) followed 59 patients receiving venlafaxine over 6 months. Seventy percent of these patients completed the study, and the response rate, determined by a 50% reduction in the HRSD score, was 81%. In another cohort study, Mitchell et al. (1005) found response rates at 8 weeks to be 52.6%, measured by the MADRS, among 312 patients with treatment-resistant illness taking venlafaxine in an open-label trial. Response rates at 10 months as measured by the MADRS increased to 73% in 149 patients who continued treatment in an extension phase of the study (1006).

Fewer studies have been conducted with desvenlafaxine; however, meta-analysis shows that it also is efficacious in the acute treatment of major depressive disorder (99). In the nine randomized, double-blind, placebo-controlled 8-week long trials with desvenlafaxine, there were 1,342 subjects in fixed dose study arms (50, 100, 200, or 400 mg/day), 463 subjects in flexible dose study arms

(100–400 mg/day), and 1,108 subjects in placebo study arms. Desvenlafaxine showed greater efficacy than placebo in rates of response as well as remission, with no greater benefit (and greater discontinuation rates) at doses greater than 50 mg daily. Overall rates of treatment discontinuation due to adverse effects were 3% for placebo and 12% for desvenlafaxine (168). Treatment emergent adverse effects included transient nausea and erectile dysfunction in men. Mean blood pressure was statistically increased in the desvenlafaxine group, but this change was clinically significant in only 2% of desvenlafaxine subjects, compared with 1% of the placebo group.

### c. Other antidepressant medications

#### 1. *Bupropion*

Meta-analyses of controlled trials have shown that bupropion is superior to placebo and is generally comparable in efficacy to both TCAs and SSRIs (105, 169, 1007). All three formulations of bupropion are superior to placebo (106), and early studies with the immediate-release formulation found it to be generally comparable in efficacy to the TCAs (105, 1008–1011). The newer sustained-release and extended-release formulations have been primarily compared with the SSRIs, and meta-analyses have established comparable efficacy (169, 1012).

Several studies have compared bupropion sustained release (SR) to SSRIs and placebo. A randomized controlled trial by Croft et al. (1013) compared bupropion SR to sertraline and placebo over 8 weeks of treatment and found both drugs to have efficacy superior to placebo. Bupropion SR had a lower rate of sexual dysfunction than sertraline. These findings were confirmed in a 16-week study that again compared bupropion SR with sertraline and placebo (1014). Another 8-week study found bupropion SR, but not sertraline, to be superior to placebo and again documented lower rates of sexual dysfunction with bupropion SR than sertraline (1015). Similar results were found when bupropion SR was compared with other SSRIs. One study comparing bupropion SR with paroxetine found equivalent efficacy (1016). In another trial, with approximately 150 patients in each arm, bupropion had similar efficacy to fluoxetine with a significantly lower burden of side effects (1017). Lower rates of sexual dysfunction have also been found with bupropion compared with sertraline (1013–1015) or paroxetine (1016). A survey of 6,297 patients in primary care settings found the incidence of sexual dysfunction with bupropion to be 22%–25%. This incidence was comparable to the incidence with nefazodone (28%) but lower than that with SSRIs and venlafaxine (36%–43%) (1018). Several small studies have examined whether bupropion might serve as a potential treatment

for SSRI-induced sexual side effects, with varying results (132, 1019, 1020).

Bupropion has also been studied as a treatment for anxiety associated with major depressive disorder. In one large trial, patients were randomly assigned to receive bupropion SR (N=234), sertraline (N=225), or placebo (N=233). Patients treated with bupropion SR or sertraline experienced significantly greater relief from anxiety symptoms than those who received placebo. Compared with sertraline, bupropion appeared to be associated with similar relief of anxiety in patients with major depressive disorder (1021).

Bupropion has also been shown to reduce the risk of relapse following successful antidepressant treatment with bupropion. In a 44-week double-blind trial of bupropion responders (1022), patients were randomly assigned to continue taking bupropion or change to placebo. Continued treatment with bupropion after acute phase response reduced the risk of relapse, compared with placebo, with few differences in side effects reported between the two groups.

#### 2. *Mirtazapine*

The efficacy of mirtazapine has been established in placebo-controlled studies (1023, 1024), two individual studies versus venlafaxine (1025, 1026), and in meta-analyses of studies comparing it to TCAs (1027–1029) and SSRIs (1030). Quitkin et al. (1030) analyzed three studies comparing patients with major depressive disorder treated with mirtazapine (N=289) to patients treated with fluoxetine or paroxetine (N=285). Although mirtazapine and SSRIs had similar efficacy over 6–8 weeks, a greater proportion of patients had onset of therapeutic benefit at week 1 with mirtazapine as compared with an SSRI (13% versus 6%). In a meta-analysis by Watanabe et al. (1031), mirtazapine was superior to SSRIs in response and remission rates at 2 weeks (12 trials), although it was comparable to SSRIs at the end of treatment (6–12 weeks). In a subgroup analysis, mirtazapine produced greater response than paroxetine (three trials) and venlafaxine (two trials). At 2 weeks as well as at the end of 6–12 weeks' treatment (8 trials used to obtain outcomes), mirtazapine had comparable efficacy to TCAs. A meta-analysis of six studies (1027) found mirtazapine to have comparable efficacy to amitriptyline over 6–8 weeks, with both drugs showing superiority to placebo.

Several randomized controlled trials have compared mirtazapine to SSRIs. Benkert et al. (1032) randomly assigned patients with major depressive disorder to treatment with mirtazapine (N=127) or paroxetine (N=123) over 6 weeks, and Wade et al. (1033) randomly assigned 197 primary care patients with HAM-D scores of at least 18 to mirtazapine (N=99) or paroxetine (N=98) over

24 weeks of treatment. In both studies, the treatments had equal efficacy at study endpoint, but mirtazapine demonstrated a different profile of side effects. Another trial randomly assigned elderly depressed patients (at least age 65 years) to mirtazapine ( $N=126$ ) or paroxetine ( $N=120$ ) over 8 weeks (1034). Compared with paroxetine, mirtazapine showed a greater benefit at day 14, had less attrition for side effects, and was significantly more effective in improving sleep. It was also more effective in reducing HAM-D scores by the study endpoint, although response and remission rates were not significantly different. Two randomized trials, one 8 weeks long ( $N=299$ ) (1035) and the other a 6-week study ( $N=132$ ) in Chinese patients, have compared treatment with mirtazapine to fluoxetine and found no differences in overall efficacy, although the onset of improvement and side effect profiles differed as with paroxetine. A similar pattern of outcomes was also observed when mirtazapine was compared with citalopram ( $N=270$ ) in an 8-week trial (1036) and when an oral disintegrating form of mirtazapine was compared with sertraline ( $N=345$ ) in another 8-week trial (1037).

Mirtazapine has also been compared with venlafaxine (both immediate release [IR] and extended release [XR] forms) in randomized controlled trials. In an 8-week trial, Guelfi et al. (1025) followed patients with major depressive disorder (HAM-D scores of at least 25) receiving mirtazapine ( $N=78$ ) and venlafaxine IR ( $N=79$ ). Mirtazapine and venlafaxine did not differ significantly in depression outcomes, although sleep was better with mirtazapine, and significantly more patients taking venlafaxine IR (15%) dropped out due to side effects, compared with patients taking mirtazapine (5%). A similar 8-week trial (1026) found no significant differences in final outcome or tolerability between venlafaxine XR and mirtazapine, although mirtazapine showed greater benefit during the first 15 days of therapy.

Patients with major depressive disorder who were not responsive or who were intolerant of two prior treatments with antidepressants were randomly assigned to treatment with mirtazapine ( $N=114$ ) or nortriptyline ( $N=121$ ) for up to 12 weeks as part of the STAR\*D trial (471). Remission rates were 12% for mirtazapine and 20% for nortriptyline. There were no significant differences in any outcome measure, and the medications were comparably tolerated. Neither mirtazapine nor nortriptyline was particularly effective as monotherapy for patients who had not benefited from two consecutive treatment trials.

Mirtazapine has been shown to decrease rates of relapse following acute phase treatment. Thase et al. (1038) compared 78 patients who received mirtazapine to 78 patients who received placebo over 9 months following an 8- to 12-week treatment with an antidepressant. Patients

taking mirtazapine had about a 50% reduction in relapse rates. However, patients taking mirtazapine gained 1.4 kg more weight than those taking placebo across the 9 months of continuation phase therapy.

### **3. Nefazodone and trazodone**

The efficacy of nefazodone has been established in placebo-controlled trials, with efficacy comparable to both TCAs and SSRIs (105, 1039–1042); however, its recent use has been limited after case reports suggested a risk of rare but potentially fatal hepatotoxicity (180). While an early review of trazodone (114) concluded that trazodone is as effective as TCAs in the treatment of depression, other investigators have found trazodone to be less effective than other antidepressant medications (115, 1043–1045), a conclusion supported by the results of at least one meta-analysis (93). In a review of 18 studies from 1980 through 2003, Mendelson (173) found that trazodone, when compared with various control groups, did improve sleep. However, it was also associated with significant side effects, and tolerance may develop with prolonged use.

### **d. Tricyclic antidepressants**

Since the first trial in which a tricyclic compound (imipramine) was shown to improve major depressive disorder symptoms (1046), hundreds of subsequent randomized controlled trials have demonstrated the efficacy of this antidepressant class as a treatment for major depressive disorder (105). Several reviews of this early literature suggested that approximately 50%–75% of patients with major depressive disorder treated with tricyclic and related antidepressant medications respond, compared with 25%–33% of patients who receive placebo (487, 1047–1049). The efficacy of individual agents and subclasses of tricyclics (e.g., secondary amines or tertiary amines) appears to be comparable, although amitriptyline may possess a slightly stronger effect across all studies (1050), and the tertiary amine tricyclics (amitriptyline, clomipramine, and imipramine) may have a stronger antidepressant effect than the secondary amine tricyclics and maprotiline in studies of hospitalized depressed patients (117).

The meta-analysis of Barbui et al. (1050) reviewed 181 randomized controlled trials of amitriptyline, generally of 6–8 weeks' duration, in inpatient and outpatient settings. Amitriptyline was found to be superior to SSRIs in studies of inpatients, but there was no difference in efficacy in outpatients. Selective serotonin reuptake inhibitors were better tolerated. Arroll et al. (1051) compared TCAs with SSRIs in a meta-analysis of 15 randomized controlled trials in primary care settings. Both TCAs and SSRIs were effective, but tolerability comparisons across studies favored SSRIs. Wohlfarth et al. (1052) reviewed 30 random-

ized controlled trials conducted between 1979 and 1991, with a combined sample size of 1,555 men and 2,331 women. Tricyclic antidepressants were more effective than placebo across age and gender groups.

Several trials have compared TCAs against interpersonal therapy and CBT and against the combination of TCAs and IPT or CBT. Reynolds et al. (1053) followed 80 patients who were at least age 50 years and had a bereavement-related depression in a 16-week factorial design trial in which patients received IPT or case management and nortriptyline or placebo. Nortriptyline (with or without IPT) was more effective than placebo (with or without IPT). Patients receiving combined nortriptyline and IPT had the highest study completion rate. Interpersonal psychotherapy alone (i.e., IPT plus placebo) was not found to be an effective treatment for bereavement-related major depressive disorder. However, in a continuation trial (N=107) over 24 months (315), combination therapy was found to be more effective than monotherapy in patients age 70 years or older. All patients had been first stabilized on combination nortriptyline and IPT before entering the continuation phase. In a 16-week randomized controlled trial among 102 elderly patients with major depressive disorder, Thompson et al. (1054) found that combined treatment with CBT and nortriptyline was superior to CBT alone, which was superior to nortriptyline alone. Combined treatment was particularly effective in patients with severe depression, as measured by HAM-D scores.

For patients with major depressive disorder who received ECT following a prior nonresponse to treatment with an antidepressant, van den Broek (1055) found that 12 patients randomly assigned to receive imipramine (200–300 ng/mL plasma level) had a greater improvement in all measures in preventing relapse than the 15 patients randomly assigned to receive placebo.

Results of some investigations have suggested that TCAs are particularly effective for patients with more severe symptoms of major depressive disorder (1056–1060), as well as for patients with melancholia (562, 1061–1063). Superior efficacy for TCAs, compared with SSRIs, has been documented in meta-analyses of inpatient studies (117).

#### e. Monoamine oxidase inhibitors

Monoamine oxidase inhibitors have also been shown in multiple trials to be effective treatments for major depressive disorder. Although some earlier comparisons employing lower doses of MAOIs found TCAs to be superior, MAOIs are now considered to have comparable efficacy to TCAs for most patients with major depressive disorder (119, 120, 1064–1067). Results of several investigations suggest that MAOIs may be particularly effective in treat-

ing subgroups of patients with major depressive disorder with atypical features such as reactive moods, reversed neurovegetative symptoms, and sensitivity to rejection (572, 1068, 1069). Monoamine oxidase inhibitors have also been shown to be effective treatments for some patients who have not responded to other antidepressant medications (1064, 1067, 1070, 1071).

In more recent controlled trials, 6 mg/24 hours of transdermal selegiline was compared with placebo in 177 adults with major depressive disorder in a 6-week trial (1072). The transdermal patch was found to be more effective than placebo and was well tolerated without the need for dietary restrictions. These findings were replicated in two subsequent studies by Amsterdam (124) (N=365; dose, 6 mg/24 hours; duration, 6 weeks) and Feiger et al. (125) (N=265; dose, 6–12 mg/24 hours; duration, 8 weeks).

Tranylcypromine in doses of 30–60 mg/day has been compared with the combination of venlafaxine IR (up to 300 mg/day) and mirtazapine (up to 60 mg/day) in 109 patients with treatment-resistant depression in a 12-week randomized trial (121). Neither the MAOI (7% remission rate) nor the combination strategy (14% remission rate) were particularly effective in this group of difficult-to-treat depressed patients, although efficacy was compromised by the use of low tranylcypromine doses. Monoamine oxidase inhibitor therapy was significantly less well tolerated and had a significantly higher dropout rate.

Limited evidence suggests that the nonselective MAOIs have comparable efficacy. Tranylcypromine and phenelzine were found to have similar response rates (44% and 47%, respectively) in a 5-week trial of 77 patients with severe major depressive disorder who had been nonresponsive to a TCA or SSRI medication (1073). Clinical experience suggests that some patients who fail to benefit from one of these MAOIs may benefit from a different one—after allowing a several-week period of washout.

## 2. Electroconvulsive therapy

The efficacy of ECT has been demonstrated in multiple clinical trials, including trials of real versus sham ECT. In a meta-analysis of the efficacy of ECT in the treatment of depressive disorders, the six trials (256 patients) that included sham ECT controls yielded a standard effect size of 0.91 favoring real ECT, consistent with a strong effect of active ECT (235). In the one sham ECT study that used unilateral ECT, no difference was found, but the treatment was not delivered sufficiently above the seizure threshold to be effective (236). In comparison with pharmacotherapy, meta-analyses similarly show an advantage for ECT with a standard effect size of 0.80 across 18 trials

(1,144 participants) (235). Comparisons of ECT against specific antidepressant classes show ECT to be superior to SSRIs, TCAs, and MAOIs (236, 425). In terms of technical aspects of ECT administration, meta-analyses show a more substantial effect of bilateral ECT than unilateral ECT (236), with a standard effect size of 0.32 for 22 trials and 1,408 participants (235). However, many of the included studies did not adjust the stimulus doses of ECT to account for differences in seizure threshold across patients, which may have increased the apparent benefit of bilateral ECT. When stimulus dosing was assessed, higher stimulus doses relative to the patient's seizure threshold were associated with greater benefit than stimulus doses closer to the seizure threshold (standard effect size = 0.73 for seven trials and 342 participants) (235). The efficacy of ECT given twice weekly did not differ from that of ECT given 3 times/week (236).

Much information about ECT response and specific factors that predict response has come from the Consortium for Research in ECT (CORE) study, a large trial funded by the National Institute of Mental Health (NIMH) in which continuation pharmacotherapy was compared with continuation ECT. In the acute phase of that trial in which 253 patients were treated with bitemporal ECT 3 times/week, 79% of the sample had an acute sustained response, with remission occurring in 75% of patients after ECT (mean number of treatments =  $8 \pm 3$ ). Response to ECT occurred rapidly, with over one-half of patients showing response by the end of the first week of treatment (240). Suicidal ideation also resolved rapidly during the course of ECT, with substantial resolution in 38% by the end of the first week, 61% by the end of the second week, and 80% by the end of the treatment course (243). Individuals who were older (715) or who exhibited psychosis (241) or atypical features (578) had a greater likelihood of achieving remission, although the presence of melancholic features was not associated with a greater likelihood of response (499). Also, unlike prior studies that had shown reduced rates of remission with ECT in patients with treatment-resistant depression (1074, 1075), the CORE study found that neither resistance to antidepressants as a whole nor resistance to any specific class of antidepressants was associated with an altered response to ECT (426).

In contrast to the high rates of ECT response found in the CORE study and in meta-analyses of clinical efficacy trials, ECT appears to have a lower rate of response when delivered in community settings. Prudic et al. (237) examined clinical outcomes following ECT and over 6 months of follow-up in 347 patients who received ECT at one of seven hospitals in the New York metropolitan area. Remission occurred in only about one-third to one-half of the sample, and two-thirds of those with remission expe-

rienced a relapse during the follow-up period. Having residual symptoms, psychotic features, or a co-occurring personality disorder conferred a heightened risk of relapse.

Other studies have delineated technical factors relating to the efficacy of ECT, including stimulus intensities and electrode placements. Sackeim et al. (253) randomly assigned 96 depressed patients to treatment with a bitemporal or right unilateral electrode placement at a low dose or high dose relative to the patient's seizure threshold. Patients treated with bilateral ECT had comparable response rates regardless of stimulus dose (65% for low dose versus 63% for high dose), whereas patients receiving low-dose right unilateral ECT had only a 17% response, and those receiving high-dose right unilateral ECT had an intermediate response (43%). In a subsequent randomized double-blind study of 80 depressed patients, an even higher dose of right unilateral ECT was used (500% above the seizure threshold). At this stimulus dose, right unilateral ECT showed comparable efficacy to bilateral ECT (65%) and superior efficacy to right unilateral ECT given at 50% or 150% above seizure threshold, for which the response rates were 35% and 30%, respectively. That high-dose right unilateral ECT has comparable benefits to bilateral ECT has also been shown in two randomized studies by McCall et al., one of which included 77 patients and used right unilateral ECT at eight times the seizure threshold (1076) and one of which included 72 patients and used a high fixed dose of 403 millicoulombs for right unilateral ECT (1077).

Several smaller studies have examined bifrontal electrode placement in comparison with bitemporal or right unilateral electrode placements. Bailine et al. (1078), who studied 48 patients with scores of 17 or higher on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17) who were randomly assigned equally to receive bifrontal or bitemporal ECT (mean number of treatments =  $6 \pm 2.5$ ), reported no difference in remission rates between the two groups. Ranjkesh et al. (1079) found no difference in HAM-D scores among patients receiving at least eight sessions of bifrontal (moderate dose, N=15), bitemporal (low dose, N=15), or right unilateral (high dose, N=15) electrode placement in an Iranian inpatient sample of patients with an initial score of 16 or higher on the 24-item Hamilton Rating Scale for Depression (HAM-D-24). Similarly, Eschweiler et al. (1080) compared the effects of six right unilateral ECT treatments (250% stimulus intensity of titrated threshold) and six bifrontal ECT treatments (150% of threshold) over a 3-week period in a randomized double-blind trial of 92 patients and found no difference in response rates between the two electrode placements.

In addition to efficacy and ECT technique, the cognitive effects of ECT have been a focus of considerable study, typically as a part of studies examining various electrode placements. In terms of the time to recover reorientation after ECT, Sackeim et al. (253) found that patients receiving bilateral ECT took substantially longer to regain their orientation than patients receiving right unilateral ECT, and the time to regain orientation increased with the stimulus dose. In addition, the time to regain orientation immediately after ECT, as well as the patient's baseline cognitive status, predicted the patient's cognitive status after the ECT course and at 2-month follow-up assessment (251). Regardless of the stimulus dose of right unilateral ECT that was used, bilateral ECT was associated with more prominent effects on cognition at follow-up assessments (253, 1081). Relative to bilateral ECT (at one and one-half times the seizure threshold), high-dose right unilateral ECT (at eight times the seizure threshold) produced comparable effects on memory, and neither electrode placement produced prolonged anterograde amnesia (1076). Lisanby et al. (248) studied 55 patients with major depression in a randomized double-blind trial of bitemporal and right unilateral ECT at low and high stimulus doses and compared the patients' function on a Personal and Impersonal Memory Test with that of a parallel group of normal control subjects. Bitemporal ECT was found to cause more prominent impairments that were most notable for impersonal events and that were independent of stimulus dose or clinical outcome. Studies of other electrode placements have shown either no difference (1080) or beneficial effects (1078, 1079) of bifrontal electrode placement relative to bitemporal electrode placement. Another factor that may relate to memory dysfunction is the number of ECT treatments administered per week, with two studies showing less prominent amnesia with twice-weekly ECT rather than ECT given 3 times/week (1082).

The cognitive effects observed in naturalistic community settings also appear to differ from those observed in research trials (252). The seven hospitals in the community study showed considerable variation from one another immediately after ECT and at the 6-month follow-up assessment. These differences seemed primarily related to differences in ECT technique across sites, with use of sine wave stimulation and bilateral ECT being associated with greater and more persistent cognitive effects on several cognitive measures, compared with brief pulse and right unilateral ECT. Given the lower efficacy rates for ECT that were also seen in the community sample, residual or recurrent depressive symptoms may also have contributed to the poorer cognitive outcomes. These findings suggest a need to optimize efficacy as well as minimize cognitive effects in clinical practice.

### 3. Transcranial magnetic stimulation

A substantial number of studies of TMS have been conducted, but most have had small sample sizes, and the studies overall have yielded heterogeneous results. Further complicating the interpretation of the TMS literature is the variability in stimulation intensities (relative to the motor threshold), stimulus parameters (e.g., pulses/second, pulses/session), anatomical localization of stimulation, and number of TMS sessions in the treatment course. A recent meta-analysis of 24 studies (with a total of 1,092 subjects) found that individuals with treatment-resistant depression were more likely to respond to TMS than to sham treatment (25% with TMS versus 17% with sham; NNT=6) (270). However, for active treatment and for sham treatment, remission occurred in fewer than 10% of subjects (270). Another meta-analysis that included 33 studies also found active TMS to be more effective than sham treatment in patients with major depression but also noted substantial variability across studies (271). Studies with stimulation intensities below 90% of motor threshold appeared to show less benefit (271). Based on a meta-analysis that included six independent trials of left dorsolateral prefrontal cortex TMS in a total of 195 patients, older individuals and those with treatment-resistant depressive episodes may also be less likely to respond (1083). Another meta-analysis of these six clinical trials found TMS to be no different from sham treatment overall in the treatment of major depression; however, the power within these studies to detect a difference was generally low (273). Schutter (272) also examined studies of TMS over the left dorsolateral prefrontal cortex and found an overall weighted mean effect size of 0.39 for TMS based on findings from 30 studies and 1,164 patients. This meta-analysis did not find any differences in the response of individuals with medication-resistant major depression as compared with those without documented medication resistance, nor did it find any evidence of study heterogeneity or publication bias. Multiple earlier meta-analyses also demonstrated benefits of TMS (1084–1087), but include an overlapping set of studies with those assessed in more recent meta-analyses. If anything, however, earlier studies demonstrated less efficacy for TMS than more recent studies (272, 1088). The duration of TMS effects has not been well studied, but one meta-analysis of 14 studies showed a robust response to TMS compared with sham TMS after 2 weeks of treatment (standardized mean difference = -0.35; 95% confidence interval = -0.66 to -0.04), but no statistically significant benefit of active TMS at 2-week follow-up (1089).

The largest published trial of TMS was a randomized, double-blind, multisite study of patients who had not responded to one to four prior trials of antidepressant therapy and were free of other medications at the time of the

study (268). Subjects received sham TMS ( $N=146$ ) or active TMS delivered to the left dorsolateral prefrontal cortex, 5 times/week for 4–6 weeks with 10 pulses/second and 3,000 pulses/session at 120% of motor threshold. At weeks 4 and 6 of the study there was a trend for greater improvement in MADRS scores in the active TMS group, but this result did not reach statistical significance. Rates of remission also did not differ between the two groups, although secondary outcome measures, including the HAM-D and response rates, did indicate a beneficial effect of TMS. In an open-label extension study of this trial (1090), 85 subjects who had received sham TMS showed significant reductions in MADRS scores after changing to active TMS; 42.4% of these patients met response criteria, and 20% had remission of their depressive symptoms by 6 weeks. Of subjects who had received active TMS and continued to receive an additional 6 weeks of treatment ( $N=73$ ), 26% showed a response to TMS, and 11% achieved symptom remission. Subsequent analysis of the data from these trials (274) showed that lesser degrees of treatment resistance were associated with better response to TMS. The lack of a co-occurring anxiety disorder also appeared to be associated with a better response to TMS in the open-label extension phase of the trial.

In another large multisite trial conducted in Europe, 127 subjects with treatment-resistant depression who were being treated with antidepressant medication (venlafaxine or mirtazapine) were randomly assigned to receive active ( $N=62$ ) or sham ( $N=65$ ) TMS delivered to the left dorsolateral prefrontal cortex, 5 times/week with 10 pulses/second and 2,000 pulses/session at 110% of motor threshold for 3 weeks. The two groups did not differ in their degree of improvement on the MADRS, HAM-D, or BDI scales, and a similar proportion of individuals in each group (31%) were classified as having responded to treatment (269).

Other smaller studies have compared TMS with ECT, with variable results. One of these studies showed ECT to be substantially more effective than TMS acutely in terms of HRSD scores and the proportion of responders at the end of the study, and, on the majority of outcome measures, ECT retained this benefit over TMS after 6 months of follow-up (275). In the other studies that compared TMS with ECT, rates of remission and response were comparable for the two treatments, although the response and remission rates for ECT in these studies were somewhat lower than typically reported in clinical ECT trials, and rates of response to TMS were higher than those reported in sham controlled trials of TMS (276–278, 1091). An additional randomized single-blind trial compared the responses of individuals who received 2 weeks of thrice-weekly unilateral ECT with the responses of individuals who received one unilateral ECT session and four TMS

sessions each week (1092) and found no statistically significant differences in efficacy or side effects between the two approaches. The cognitive effects of TMS and ECT have been assessed in one open study (279), in which subjects treated with TMS reported memory to be unchanged or improved approximately 9 days after the treatment course as compared with unilateral ECT, which was associated with a greater degree of subjective, retrograde, and anterograde memory difficulties shortly after the end of the treatment course. A subsequent randomized single-blind trial (276) showed no significant difference between individuals who received TMS and those who received unilateral ECT when neuropsychological performance was tested at 2 and at 4 weeks of treatment. However, there was a trend for worsened performance in those receiving ECT versus a trend for improved performance in those receiving TMS.

Analysis of aggregate safety data from more than 10,000 treatment sessions with 325 patients treated at 23 clinical sites in the United States, Australia, and Canada showed that TMS was well tolerated, with less than 5% of subjects leaving the study due to adverse effects and no seizures or deaths observed (280). The most common adverse effects were transient headaches or scalp discomfort. Overall, side effects of treatment were mild to moderate in intensity and dissipated over the initial week of treatment.

#### **4. Vagus nerve stimulation**

The FDA approved VNS for treatment-resistant depression based on efficacy data from two different samples, for which acute and longer term data are available. The first sample consisted of 60 outpatients with chronic or recurrent major depressive disorder, bipolar I disorder, or bipolar II disorder who had not responded to at least two medication trials from different antidepressant classes. This cohort was first followed in an open-label fashion with 10 weeks of active stimulation after a 2-week period to permit recovery from surgery (281). On the primary outcome measure, the 28-item Hamilton Rating Scale for Depression (HAM-D-28), 30.5% of the sample showed a response (defined as at least a 50% reduction from the baseline HAM-D-28 score) and 15.3% of the sample had a full remission of symptoms (defined as HAM-D-28 of less than 11). Response was less likely to occur in patients who had received a greater number of unsuccessful antidepressant trials or who had received ECT prior to VNS. This cohort was then followed for up to 2 years naturally, with changes to psychotropic medications and VNS stimulus parameters permitted (479). In a last-observation-carried-forward analysis, response rates were 44% and 42% after 1 and 2 years, respectively, with remission rates of 27% and 22% at 1 and 2 years, respectively (479).

A subsequent VNS trial was a multisite randomized trial with 235 participants that included an acute sham-controlled phase (282) and a longer term naturalistic follow-up phase (477) and comparison with a relatively similar treatment-as-usual sample. In the acute phase, nonpsychotic outpatients with treatment-resistant major depressive disorder ( $N=210$ ) or patients with depressed phase bipolar disorder ( $N=25$ ) received 10 weeks of active or sham treatment after 2 weeks of recovery from implantation surgery. In terms of response (i.e., at least 50% reduction in HAM-D-24 score), there was no significant difference with VNS treatment (15.2% response vs. 10% for sham). These findings may be confounded by the frequent occurrence of hoarseness or voice alteration with stimulation (281), which may have affected the blinding of the study subjects or investigators. During the longer term naturalistic follow-up phase, in which changes in medication were permitted, the active VNS group received 9 additional months of VNS, and the sham group received 12 months of VNS (282). A repeated-measures linear regression analysis of the primary outcome measure showed significant reductions in HAM-D-24 scores, with response and remission rates of 27.2% and 15.8%, respectively, at the study endpoint (282). A similar but nonrandomized treatment-as-usual group ( $N=124$ ) showed a response rate of 13%, suggesting a benefit of VNS (476).

To determine whether the benefits of VNS were durable, data from the studies described earlier in this section were combined, and the persistence of the antidepressive response was determined (478). Of individuals who had shown an early response (by 3 months of VNS), 66.7% and 64.6% of the overall group had maintained that response at 1 and 2 years, respectively. Of those who had shown a late response (by 12 months of VNS), 68.5% had maintained that response at 2 years, suggesting persistent benefits of VNS.

An additional uncontrolled multisite European trial showed somewhat lower rates of sustained response (44%) at 1 year of VNS treatment, although overall response and remission rates at 1 year were 53% and 33%, respectively (481). Other smaller, open-label trials have been recently reviewed and also show reductions in depressive symptoms when VNS is used in combination with other antidepressive treatments for individuals with treatment-resistant depression (480).

Across all studies, VNS was generally viewed as tolerable (480). Rates of study dropout were low (about 1%) during the initial 3 months of treatment (282), with about 80% of subjects continuing with VNS at the end of 2 years (479). Voice alteration or hoarseness occurred in about two-thirds of subjects in conjunction with stimulation (281). Coughing occurred in about one-quarter of individ-

uals (281), and dyspnea and neck pain were also commonly reported (481).

## 5. Complementary and alternative treatments

### a. St. John's wort

Despite a large number of trials examining St. John's wort (usually in the form of *Hypericum perforatum* extract), there is no consensus on its efficacy in major depressive disorder. A 2005 Cochrane meta-analysis (1093) provided a summary of treatment studies utilizing St. John's wort for the treatment of major depressive disorder. The published studies demonstrate heterogeneity in methods used and great inconsistency in study outcomes. A number of double-blind studies have demonstrated its superiority over placebo, although some have not (370, 371). In addition, St. John's wort may have better tolerability than TCAs and SSRIs, and several randomized studies have shown noninferiority relative to approved antidepressant medications, although the distinctive taste of St. John's wort extract may have caused some unblinding during the studies.

Among the larger and most rigorous recently published placebo-controlled trials, the studies by Shelton et al. (371) ( $N=200$ ) and Davidson et al. (370) ( $N=340$ ) did not demonstrate a difference between St. John's wort and placebo on primary outcome measures, but Lecrubier et al. (1094) found a significant difference between St. John's wort and placebo in mild to moderate depression ( $N=375$ ). In addition, a recent review of 14 short-term, double-blind trials conducted in outpatients with mild to moderate symptoms of major depressive disorder demonstrated that St. John's wort in doses of 300 mg/day and 1,800 mg/day had efficacy superior to placebo and was generally comparable to low-dose TCA treatment (e.g., 30–150 mg/day of amitriptyline) (105). Side effects were observed in a lower proportion of individuals taking St. John's wort than among those taking a TCA (25% vs. 40%) (105).

### b. S-adenosyl methionine

A number of studies have found SAMe to be efficacious in oral doses that range from 800 mg/day to 1,600 mg/day. In a double-blind trial, 15 inpatients with major depressive disorder received oral SAMe or placebo for 21 days (1095). Six of nine patients receiving SAMe demonstrated response as defined by a reduction of 50% or more in HAM-D scores, and depression ratings compared with placebo were significantly lower in the SAMe group than in the placebo group at days 14 and 21. Side effects were mild and transient. In a meta-analysis of studies comparing effects of SAMe with those of TCAs, SAMe was found to have better tolerability and greater efficacy in the treatment of depression, although the doses of TCAs were subtherapeutic in some studies (381). Data from two multicenter studies also

demonstrated that parenteral and oral formulations of SAMe were comparable in efficacy to the TCA imipramine (1096), although side effects were significantly more frequent in the imipramine-treated group. In one of the larger controlled trials, which included 293 participants, Pancheri et al. (382) found SAMe (administered intramuscularly at a dose of 400 mg/day) and imipramine (administered by mouth at a dose of 150 mg/day) to be similarly efficacious in a 4-week trial. Other studies have focused on specific subgroups of patients, such as HIV-positive patients and postmenopausal women (1097, 1098).

#### **c. Omega-3 fatty acids**

Two large meta-analyses found benefits of omega-3 fatty acids overall in mood disorder trials (384, 385) but also highlighted the heterogeneity of study designs and results. The one monotherapy study of DHA for major depressive disorder in adults did not demonstrate benefit of DHA over placebo (1099), although small trials in major depressive disorder in children and in pregnant women did demonstrate a benefit of monotherapy with omega-3 fatty acids (EPA and DHA) (1100, 1101).

#### **d. Folate**

In a study by Coppen and Bailey (389) that included 127 subjects, 94% of women who received fluoxetine and 500 mcg/day of folate responded to treatment, compared with 61% of those who received fluoxetine and placebo ( $p<0.005$ ). Patients who received folate were also less likely to report side effects ( $p<0.05$ ).

#### **e. Light therapy**

In a meta-analysis, Golden et al. (395) found clinically significant benefit of bright light therapy in seasonal major depressive disorder (eight studies), with a large effect size (0.84), and in nonseasonal major depressive disorder in three studies with a medium effect size (0.53). However, the authors, who were participants of an APA work group on the topic of light therapy, determined that many of the studies of light therapy for mood disorders had methodological flaws, including small sample sizes, with only 13% of the studies they assessed meeting the inclusion criteria for their meta-analysis. Bright light therapy in nonseasonal major depressive disorder was not found to be significantly more efficacious than placebo in trials when used adjunctively in addition to antidepressants. As determined by the APA work group, an adequate placebo condition requires a maximum dose of 300 lux (versus at least 3,000 lux-hours for an active treatment condition for bright light treatment). Randomized, placebo-controlled studies have ranged from 7–42 days in treatment duration, with provision of between 2,500–10,000 lux illuminance of white light, with delivery time between 0.5–6 hours/day. Some

published studies were found to have bright light exposure at levels too high to constitute a scientifically valid control condition, and the difficulty in creating a reasonable control condition for bright light therapy may have contributed to the limited evidence base to date. Control groups have included lower doses of white light, red light, active light avoidance, negative air ionizer, and no treatment. Despite heterogeneity of designs and results, evidence supports the efficacy of bright light as a monotherapy for acute major depressive disorder. Individualization of a regimen may be required in terms of lux, length of exposure, and time of day of delivery. In addition, patients should be monitored for emergence of mania during treatment (1102).

#### **f. Acupuncture**

Assessment of the evidence base for acupuncture is complicated by the fact that many reports are in Asian languages and therefore often overlooked by English language literature searches. Results from studies in acupuncture are difficult to interpret, because the description of the methods is often limited and there is variability in diagnosis and in interventions (403). Wang et al. (407) published a recent meta-analysis of eight trials of acupuncture and depression chosen from more than 200 studies on the basis of having a randomized design, specific diagnostic criteria for depression, and specific acupuncture interventions (manual, electro-acupuncture, or laser). The depression criteria included DSM, International Classification of Diseases, and Chinese Classification of Mental Disorders criteria. The meta-analysis did not demonstrate a benefit of acupuncture over control conditions on either response rates or remission but was based on a small number of trials with variable methodological quality. Consequently, additional systematic study is required to assess the role of acupuncture for major depressive disorder.

There have been few randomized, double-blind, placebo-controlled studies to inform the use of acupuncture for depression. In one published study, Allen et al. (405) compared 38 women, ages 18–45 years, who were assigned to three different groups: an acupuncture regimen specifically chosen to address their depression, sham acupuncture, or a waiting-list control condition. The active acupuncture group experienced a significantly greater remission rate. However, Allen et al. (406) failed to replicate these results in a larger randomized trial, in which 151 patients with major depressive disorder received acupuncture specific for depression, sham acupuncture, or a waiting-list condition. After 8 weeks, there was no evidence of benefit for the acupuncture intervention specific for depression, compared with sham acupuncture or the waiting-list condition. Response rates were 22% for the depression-specific acupuncture treatment and 39% for the sham acupuncture treatment.

In another randomized study, Luo et al. (404) compared effects of electro-acupuncture combined with placebo medication to the effects of amitriptyline in 241 inpatients. Electro-acupuncture appeared equivalent to amitriptyline at a dose of 150–175 mg/day in treating depression, with greater improvement for symptoms of anxiety, cognitive problems, and somatization; it also resulted in a lower side effect burden than amitriptyline. However, no group received the placebo medication alone, and no sham treatment was used to elucidate nonspecific benefits of acupuncture treatment.

## B. SPECIFIC PSYCHOTHERAPIES

### 1. Cognitive and behavioral therapies

#### a. Cognitive-behavioral therapy

In the three decades since its first evaluation as a treatment for major depressive disorder, CBT has been extensively studied in controlled trials. When meta-analyses have quantified the efficacy of CBT compared with no treatment or minimal treatment, effect sizes have been fairly robust, generally near or above one standard deviation in the outcome measures (514, 1103–1106). Relative to other treatments, estimates of CBT efficacy from meta-analyses have been less consistent, although effect sizes for CBT have generally been comparable to those for other short-term forms of psychotherapy (e.g., IPT and brief dynamic psychotherapy) (1107).

Factors relating to the administration of CBT may influence response. Some data suggest that the efficacy of CBT may vary depending upon the severity of major depressive disorder, with less efficacy in individuals with more severe symptoms (1108). Individuals with moderate to severe depression may need more skilled CBT therapists to achieve therapeutic benefits (67). Other trials have failed to show a differential response to treatments on the basis of initial symptom severity, possibly because of lack of statistical power (1109, 1110).

Recent research has raised questions about the relative strengths of the cognitive and the behavioral components of CBT. Dimidjian et al. (310) randomly assigned 241 patients with major depressive disorder to receive CBT, behavioral activation, paroxetine, or placebo. Among patients with more severe depression, behavioral activation had similar efficacy to medication, and both were superior to CBT. This study shows that behavioral interventions may be preferable to cognitive techniques for patients with more severe depressive symptoms.

According to a data synthesis of studies conducted between 1980 and October 2004, conducted by Hollon et al.

(363), CBT and IPT can be as effective as medications in the acute treatment of depressed outpatients. Comparable rates of medication and CBT response have also been found in a number of randomized trials. For example, Jarrett et al. (576) compared CBT to phenelzine and placebo in a 10-week randomized trial that included 108 patients with major depressive disorder with atypical features. Cognitive-behavioral therapy had comparable efficacy at achieving response (indicated by a HAM-D score of 9 or lower), and both were superior to placebo in an intent-to-treat analysis. In another study, DeRubeis et al. (67) reported that among 240 patients randomly assigned to receive paroxetine, CBT, or placebo, CBT was comparable to paroxetine but was not clearly superior to placebo at 8 weeks. In addition, at 16 weeks, CBT and paroxetine showed comparable rates of response and remission in individuals with moderate to severe major depressive disorder.

In subanalyses of the NIMH Treatment of Depression Collaborative Research Program study, CBT was less effective than imipramine plus clinical management among individuals with moderate depression (defined by scores of 20 or higher on the HAM-D or scores of 50 or lower on the Global Assessment of Functioning); there was also a trend for CBT to be less effective than IPT (1108). No differences were observed between CBT, IPT, imipramine plus clinical management, or placebo plus clinical management among less severely depressed subjects. At study endpoint as well as at 18-month follow-up, there were no significant differences among these treatment groups in degree of symptom reduction or ratings of current clinical condition. However, at the 18-month follow-up assessment, patients receiving IPT or CBT reported a significantly greater capacity to establish and maintain interpersonal relationships and to recognize and understand sources of their depression than patients in the imipramine plus clinical management group or the placebo group (1111).

Unlike medications, CBT decreases the risk of relapse even after this treatment is terminated (363), and continuing CBT in the maintenance phase further decreases this risk. In a maintenance treatment study by Paykel et al. (368), 158 patients with partial remission from a major depressive episode while taking medication were randomly assigned to clinical management or clinical management and CBT. Cognitive-behavioral therapy was given in 16 sessions over 20 weeks, with two booster sessions at 72 weeks. Relapse reduced from 47% to 29% with CBT, and CBT was associated with higher remission rates. Bockting et al. (497) also compared treatment as usual (including medication) to treatment as usual and CBT in a German outpatient sample of 187 patients. Cognitive-behavioral therapy had “significant protective effect” that increased with number

of prior episodes. For patients with five or more prior depressive episodes, CBT lowered relapse from 72% to 46%. This study suggests that psychotherapy may have a protective effect, especially for more severely ill patients.

### b. Behavior therapy

Although numerous trials have examined the efficacy of behavior therapy, relatively few have employed random assignment and adequate control conditions. Two meta-analyses found behavior therapy superior to a waiting-list control condition (observed in seven of eight trials) (487, 1107). Results of individual clinical trials have suggested that behavior therapy may be superior in efficacy to brief dynamic psychotherapy (1112, 1113) and generally comparable in efficacy to cognitive therapy (1114–1117) or pharmacotherapy (283). One post hoc examination of clinical trial data found that response to behavior therapy may be more likely in patients with less initial severity of major depressive disorder symptoms (1118), but other studies have not found this relationship (1119–1121).

More recently, “dismantling studies” comparing the full CBT package to some of its elements suggest that behavioral activation, the behavioral component of CBT, may be as efficacious or more efficacious than CBT as a whole, particularly for patients with greater depressive severity (310, 1122). Behavioral activation not only outperformed CBT and placebo with respect to more severely depressed patients, but it was as efficacious as medications regardless of severity (310) and more enduring following treatment termination (288). In addition, activity scheduling, a behavioral activation treatment in which patients learn how to increase the number of pleasant activities and interactions with their environment, was found in a meta-analysis to be an effective treatment for depression (706).

## 2. Interpersonal therapy

Like CBT, IPT was developed to treat patients with major depressive disorder and has demonstrated efficacy in a series of randomized clinical trials (1123, 1124). In the NIMH Treatment of Depression Collaborative Research Program study, IPT had greater efficacy than pill placebo plus clinical management and was comparable to imipramine plus clinical management for patients with more severe major depressive disorder, whereas cognitive therapy was not superior to placebo. Among patients with mild depressive severity (defined as scores less than 20 on the HAM-D or greater than 50 on the Global Assessment of Functioning scale), IPT, CBT, and imipramine plus clinical management did not differ from placebo plus clinical management (1108). The degree to which patient and therapist can resolve the interpersonal crisis on which IPT

focuses (e.g., a role transition) appears to correlate with symptomatic improvement (1125).

Other studies have found IPT effective in treating pregnant and postpartum women with major depressive disorder (743, 1126) and depressed patients in a developing country (351). A controlled trial of IPT has also demonstrated its effectiveness for depressed primary care patients (1127). After 8 months, the proportions of patients treated with IPT, nortriptyline, or usual care who achieved remission were 46%, 48%, and 18%, respectively. In a study of depressed HIV-positive patients, greater improvements were observed after IPT or IPT plus imipramine than after supportive psychotherapy or CBT (316). However, a large recent study found no benefit for IPT over clinical management in depressed cardiac patients (807).

Many trials have been conducted comparing IPT, both as monotherapy and augmentation, to various control conditions and active comparators, both in acute phase treatment and continuation and maintenance therapy. Generally, IPT is superior to treatment as usual and is an effective augmentation strategy for patients receiving pharmacotherapy. A meta-analysis of 13 studies of IPT conducted from 1974 to 2002 reported that, in nine of the studies, IPT was superior to placebo (1123). In addition, IPT was more efficacious than CBT. However, the combination of IPT and medications was not significantly more effective than medication monotherapy for acute or prophylactic treatment.

## 3. Psychodynamic psychotherapy

Psychodynamic psychotherapy has been used widely in clinical practice for the treatment of patients with depressive symptoms and syndromes and is sometimes preferred by patients (361). However, its efficacy in major depressive disorder has not been adequately studied in controlled trials. Using the available evidence to determine the efficacy of psychodynamic psychotherapy in the treatment of major depressive disorder is complicated by several problems. In some early studies, variants of psychodynamic psychotherapy served as a nonspecific comparison treatment to other psychotherapeutic interventions, but the details of the psychodynamic psychotherapy employed were poorly defined (1107). Subsequently, some clinical trials of psychodynamic psychotherapy have reported short- and long-term therapeutic benefits (as described in references 1128–1130), but few of these trials were randomized or assessed treatment fidelity; some included concomitant pharmacotherapy, and most studied patients with a multiplicity of symptoms and diagnoses, such as depressed patients who did not meet the DSM-IV criteria for major depressive disorder. These limitations make it

difficult to draw conclusions from meta-analyses that incorporate a variety of study populations and designs (286, 1130, 1131). A recent meta-analysis (1132) acknowledged that the quality of available studies on psychodynamic psychotherapy for treatment of depression was not optimal. In addition, use of low-quality studies in meta-analyses of psychotherapy may lead to overestimations of effect sizes (1133). With these caveats, some findings from meta-analyses of short-term (1132) and long-term (1130) psychodynamic psychotherapy suggest possible benefits in individuals with depressive symptoms (1132) and suggest that long-term psychodynamic psychotherapy may have beneficial effects in individuals with depressive and anxiety symptoms (1130). To confirm these results and extend them to individuals diagnosed with major depressive disorder, further research with more rigorous study designs will be needed.

#### 4. Marital therapy and family therapy

Reviews have concluded that marital therapy is effective for treating depressive symptoms and reducing risk for relapse (1134, 1135). In a recent meta-analysis of eight marital therapy trials, marital therapy had comparable efficacy to individual psychotherapy for the treatment of depression (1136). A lower dropout rate was found for marital therapy than for medication therapy, although this result was heavily influenced by a single study. Marital therapy was superior in treating depressive symptoms, compared with minimal or no treatment. These findings were weakened by methodological problems affecting most studies, such as the small number of cases available for analysis in almost all comparisons, and the significant heterogeneity among studies.

Results from individual studies suggest that the efficacy of marital therapy may depend on whether marital distress is present. In one study, a greater proportion of depressed subjects with marital distress responded to marital therapy than to cognitive therapy (88% vs. 71%), but among depressed subjects without marital distress, a greater proportion responded to cognitive therapy than to marital therapy (85% vs. 55%) (1137). In another study of depressed subjects with marital discord, marital therapy and CBT were equally effective and both were more effective than a waiting-list condition (1138). A pilot randomized trial found “conjoint” (marital) IPT for depressed married women equipotent to individual IPT in alleviating depression and superior in improving marital satisfaction (1139).

A randomized controlled trial of antidepressant drug therapy in comparison to couple therapy for depressed outpatients found a lower dropout rate and greater improvement in subjective symptoms of depression, at no greater cost, for the couple therapy group (342). Patients recruited

during a psychiatric hospitalization for major depressive disorder were randomly assigned to pharmacotherapy alone; combined pharmacotherapy and cognitive therapy; combined pharmacotherapy and family therapy; and combined pharmacotherapy, cognitive therapy, and family therapy. Patients who received treatment that included a family therapy component were more likely to improve and had significant reductions in interviewer-rated depression and suicidal ideation, compared with those whose treatment did not include family therapy (343).

#### 5. Problem-solving therapy

Some studies have reported modest improvement in subjects with mild depressive symptoms treated with problem-solving therapy. For example, Dowrick et al. (1140) treated 452 subjects with depressive or adjustment disorders, comparing groups that received eight sessions of problem-solving therapy to control groups given six sessions of group preventive education. At 6 months, the authors found a 2.6-point difference on the BDI favoring problem-solving therapy (NNT=6). Treatment effects at 1 year did not differ. Problem-solving therapy may have advantages over usual care for home-bound geriatric patients with depressive symptoms (1141). Unfortunately, usual care often means little care.

Alexopoulos et al. (335) reported that 12 sessions of problem-solving therapy were superior to supportive psychotherapy for depressed geriatric patients with major depressive disorder and executive dysfunction. Another study showed problem-solving therapy to have greater benefit than usual care in preventing depression (1142).

#### 6. Group therapy

A mostly European body of research suggests that the individual psychotherapies validated in treating depression also work in group format. Most of these studies have sought to demonstrate efficacy rather than exploring the technical aspects of group therapy.

Group cognitive therapy has shown benefits in the acute treatment of major depressive disorder. For example, Ayen and Hautzinger (347) randomly assigned 51 depressed, menopausal women for 3 months of weekly, 2-hour sessions of cognitive group therapy, of group supportive psychotherapy, or a waiting list. Both active treatments were well tolerated and relieved depressive and menopausal symptoms better than the control condition. At 1-year follow-up, group CBT was more beneficial than group supportive therapy. In contrast, group CBT was ineffective in treating dysthymic disorder. Ravindran et al. (293) found sertraline superior to placebo but 12 weeks of group CBT no better than placebo and ineffective in augmenting sertraline in treatment of patients with dysthymia.

McDermut et al. (1143) conducted a meta-analysis of 48 research reports assessing the efficacy of group therapy for the treatment of depression in individuals with various types of depressive disorders (depressive spectrum disorders). Analyses suggested that participants in treatment showed significant clinical improvement.

Forms of group CBT have also shown promise in lowering relapse risk. Bockting et al. (497) reported that for the 41% of 187 patients with remission who had a history of at least five episodes of recurrent major depressive disorder, augmenting usual treatment with brief group CBT lowered relapse rates from 72% to 46% over a 2-year period.

Teasdale et al. (498) found that group mindfulness-based cognitive therapy as an augmentation strategy was beneficial relative to treatment as usual in reducing relapse rates over 60 weeks for 145 patients with recurrent depression who reported at least three prior major depressive episodes.

Interpersonal psychotherapy has also been adapted to a group format (1144). Although IPT is less well studied than CBT, small trials of group IPT suggest its benefits as both a preventive intervention (350) and a treatment for postpartum depression (349). A group combining interpersonal and cognitive elements improved outcome relative to fluoxetine alone among patients with dysthymia who responded to fluoxetine (1145).

## C. PSYCHOTHERAPY COMBINED WITH PHARMACOTHERAPY

Although many psychiatrists prefer to use a combination of psychotherapy and pharmacotherapy to treat patients with depression, controlled studies conducted in the 1970s and 1980s did not consistently find a significant advantage for routinely combining therapies, compared with one or the other treatments provided alone (1146). Part of the problem in establishing the additive value of psychotherapy and pharmacotherapy in these early studies was methodological: the specific effects of each modality (i.e., over and above the so-called nonspecific effects of therapeutic support and placebo-expectancy factors) are relatively modest, and none of the early studies of combined therapy had the statistical power to reliably detect such small effects. Consistent with this appraisal, a meta-analysis of these early studies found an average effect size of about 0.3 (1147), which is both a clinically significant effect and an advantage that would usually not be found to be statistically significant in a study of 100 or fewer patients. A meta-analysis of individual patient data performed by Thase et al. (359), which compared remission rates of nearly 600 patients treated in studies of CBT, IPT, and IPT in combination

with either imipramine or nortriptyline, confirmed a modest overall advantage for combined treatment versus CBT or IPT alone but found a differential impact linked to severity and history of recurrent depressive episodes. Specifically, whereas combined treatment had a small advantage over psychotherapy alone among patients with less severe depression, there was a fourfold difference in remission rates among the subset of patients with more severe, recurrent depressive episodes.

The advantage of combined treatment over pharmacotherapy alone in more severe depression was evident in a well-controlled inpatient study of Schramm et al. (285). Conducted in Germany, this 5-week trial included 124 hospitalized patients with major depressive disorder; results showed a 70% response rate to IPT plus pharmacotherapy, compared with a 51% response rate to pharmacotherapy alone. In a Swiss study in which 74 outpatients were randomly assigned to receive 10 weeks of clomipramine plus psychodynamic therapy or clomipramine alone, the combination treatment produced greater improvements in global functioning, greater cost savings, lower rates of hospitalization, and fewer lost work days (1148).

Keller et al. (362) examined the outcomes of more than 600 patients with chronic depression who were randomly assigned to treatment with the antidepressant nefazodone or a form of CBT (cognitive behavioral analysis system of psychotherapy [CBASP]) singly or in combination. The authors found a large additive advantage for the two treatments in combination. Specifically, response rates for combined treatment were approximately 20% higher at the end of 12 weeks of treatment, compared with the monotherapies, which were comparably effective. It is noteworthy that patients receiving combined treatment experienced the earlier benefit that characterized the pharmacotherapy as well as the later emerging benefit that characterized the psychotherapy (362). A post hoc analysis of these results revealed that the advantage of the combined approach was explained by a broader spectrum of efficacy: pharmacotherapy alone was significantly less effective than CBASP among the subset of patients with a history of childhood trauma, whereas the opposite trend was evident among the patients treated with psychotherapy alone (1149). Patients with chronic depression were thus more likely to benefit from combined treatment whether or not they had a history of early adversity.

In the STAR\*D study, patients with depression who did not have remission following an initial 12-week course of citalopram therapy were offered the opportunity to add or change to Beck's model of cognitive therapy in addition to the various pharmacotherapy options being studied. Among those who opted to add a therapeutic adjunct to ongoing citalopram, about one-third consented to be ran-

domly assigned to strata that included both cognitive therapy and medications (buspirone or bupropion). Results at the end of 12 weeks of therapy indicated that cognitive therapy was as effective as medication augmentation, although patients opting for combined pharmacotherapy responded faster (369).

One historic limitation of the literature on combined treatment of depression has been that a vast majority of studies have concerned cognitive therapy and IPT, and there has been a dearth of studies on the more widely practiced forms of psychodynamic psychotherapy. An informative series of studies by one group of investigators in the Netherlands has helped to partly address this issue. The first trial compared outcomes of 167 outpatients with depression across 6 months of treatment with either algorithm-guided antidepressant pharmacotherapy alone or pharmacotherapy combined with a manual-based form of time-limited dynamic psychotherapy (1150). Significant differences favored combined treatment with respect to retention in treatment and the likelihood of remission. A secondary analysis determined that the advantage of combined treatment was largely explained by the large difference among patients with co-occurring Axis II disorders (1151). In a second study of 191 depressed outpatients, time-limited dynamic therapy alone was compared against psychotherapy in combination with algorithm-guided pharmacotherapy (1152). In this trial, there were significant differences favoring combined therapy on patient-rated outcomes, although the numeric difference between groups on remission rates was not statistically significant. The investigators next conducted a pooled analysis of the data from these two trials, also including a third smaller study that did not include a combined therapy arm (361). The analysis included data for more than 300 depressed outpatients and confirmed the advantage of combined treatment over the monotherapies across studies on most outcome variables.

Two meta-analyses of study results have confirmed the advantage of combining pharmacotherapy and various forms of time-limited psychotherapies (360, 1153). The latter report confirmed that the advantage was larger among studies of patients with more severe symptoms and among those with more chronic depressive disorders (1153).

## D. LACK OF RESPONSE TO PHARMACOTHERAPY IN THE ACUTE PHASE

### 1. Maximizing initial treatments

Several studies have shown improved efficacy with higher doses of medication, supporting the strategy of increasing the medication dose for patients who do not respond to an

initial trial of a medication. As an example, Bech et al. (1154) conducted a randomized controlled trial in which patients meeting the criteria for major depressive disorder were randomly assigned to receive placebo or citalopram in doses of 10 mg/day (N=129), 20 mg/day (N=130), 40 mg/day (N=130), or 60 mg/day (N=129). Treatment continued for 6 weeks, and depressive symptoms were measured by 21-item Hamilton Rating Scale for Depression, MADRS, Clinical Global Impression, and 56-item Symptom Checklist. The percentages of patients lost to follow-up were 9% for placebo, 7% for citalopram at 10 mg/day, 2% for citalopram at 20 mg/day, 2% for citalopram at 40 mg/day, and 3% for citalopram at 60 mg/day (nonsignificant p values). The 10- and 20-mg doses were more efficacious than placebo, but they were inferior to the 40- and 60-mg doses ( $p<0.05$ ). The 20-, 40-, and 60-mg doses had significantly more side effects than placebo, measured by dropout rates due to side effects ( $p<0.05$ ).

### 2. Changing to other treatments

The recently completed STAR\*D trial examined various strategies for patients with treatment-resistant depression. STAR\*D was a multisite, multistep, prospective randomized controlled trial comparing treatments and treatment strategies in outpatients with major depressive disorder (48). The study provided data on treatment effectiveness, or “real world” outcomes in typical patients, making the results generalizable to standard practice. The study was organized into four levels. In level 1, 2,876 outpatients received citalopram for up to 14 weeks. In level 2, nonresponders (N=1,493) were offered three alternatives, which were selected based on patient choice: change to another medication (N=727), augment citalopram with another medication (N=565), or start psychotherapy (N=147). If the patient changed to another medication, he or she was randomly assigned to receive sertraline, bupropion SR, or venlafaxine XR. Patients who chose medication augmentation were randomly assigned to augment citalopram with bupropion SR or buspirone. Patients who agreed to start psychotherapy were randomly assigned to change to cognitive therapy (discontinuing citalopram) or to augment with cognitive therapy (continuing citalopram). For patients who did not respond to level 2, level 3 offered two alternatives: changing or augmenting with another medication. Patients in the change group were randomly assigned to receive mirtazapine (N=114) or nortriptyline (N=121) for up to 14 weeks. Patients in the augmentation group were randomly assigned to receive lithium (N=69) or triiodothyronine (N=73) for up to 14 weeks. Finally, level 4 randomly assigned nonresponders from level 3 to receive tranylcypromine (N=58) or the combination of

venlafaxine XR and mirtazapine ( $N=51$ ). STAR\*D therefore provides data for several randomized controlled trials of change or augmentation of medications at various stages. Two such studies based on STAR\*D data provide evidence for continued efficacy of medication augmentation (429) and medication change (471) for treatment-resistant depression. Remission rates were equivalent and approximately 25% upon changing from citalopram to either an SSRI or SNRI or bupropion at the second step; there was no difference in remission between changing to either mirtazapine or nortriptyline at the third step.

A number of previous studies evaluated changing from an SSRI to another SSRI, changing from an SSRI to an SNRI, and changing from an SSRI to bupropion or mirtazapine. These previous studies were either small in size or, in the vast majority of instances, were neither randomized nor blinded. A few trials have been conducted in which patients who did not respond to an initial antidepressant medication were changed to a non-MAOI antidepressant medication from the same pharmacological class (e.g., from one TCA to another) or to one from a different pharmacological class (e.g., from a TCA to an SSRI). Although results from these trials have been variable, up to 50% of patients have been found to respond (i.e., have symptom improvement of at least 50%) to a second non-MAOI antidepressant medication trial—even when the second antidepressant was from the same class as the first (421). Data regarding the types of treatment-resistant patients who are most likely to benefit from particular changes in medication are limited.

### **3. Augmenting and combining treatments**

Traditionally, augmentation agents with the most evidence for efficacy have included lithium and thyroid hormone for partial responders to traditional antidepressant medications (1155). Recent studies have significantly advanced the literature now with the two augmentation randomized controlled trials in STAR\*D (429, 446) and the use of adjunctive aripiprazole (453, 1156). In the most recent large-scale trial—a component of the STAR\*D study—lithium augmentation of citalopram was neither particularly well tolerated nor more effective than thyroid augmentation (446).

The second-step augmentation trial in the STAR\*D study evaluated the comparative efficacy of add-on sustained-release bupropion and add-on buspirone in patients who had not achieved adequate remission status following an initial trial with citalopram. Both agents as adjuncts were associated with remission rates of around 30% on primary outcome measures. Patients who did not have remission with up to 12 weeks of citalopram therapy were as likely to benefit from adjunctive buspirone

(15–60 mg/day) as they were to benefit from adjunctive bupropion (150–400 mg/day) (429). However, adjunctive treatment with bupropion SR was superior to adjunctive buspirone on a number of key secondary measures (224).

The findings of 16 placebo-controlled, randomized clinical trials of second-generation antipsychotic augmentation therapy for patients with major depression disorder ( $N=3,480$ ) have recently been evaluated in a meta-analysis (448). Augmentation with a second-generation antipsychotic agent was significantly more effective than placebo in terms of rates of response and remission. Although aripiprazole has received FDA approval as an adjunct to second-step antidepressant medications for patients who had not achieved satisfactory response to at least two prior antidepressant medication trials, this meta-analysis showed no differences in response or remission rates among the individual medications (448). Discontinuation rates for adverse effects were also higher in the active augmentation groups compared with placebo, suggesting that such effects need to be taken into consideration when choosing to augment antidepressant response with a second-generation antipsychotic agent. To date, few data from controlled studies address the longer term efficacy or side effects of combining antidepressants and antipsychotics.

Combining an SSRI and a TCA induced a rapid antidepressant response in one preliminary study (1157). In a second study, patients taking this combination also had a greater likelihood of remission, compared with patients receiving monotherapy with an SSRI or a TCA (1158). The efficacy of combining mirtazapine and an SSRI was demonstrated in one placebo-controlled study (432). Mirtazapine and venlafaxine led to a 13.7% remission rate in patients who had not responded to three prior medication trials as part of the STAR\*D study (121). Case reports suggest that stimulant medications may be effective adjuncts to antidepressant medication therapy (205), although the results of larger scale clinical trials have not demonstrated efficacy (462, 463).

### **E. CONTINUATION TREATMENT**

Although randomized controlled trials of antidepressant medications in the continuation phase are limited, the available data indicate that patients treated for a first episode of uncomplicated major depressive disorder who exhibit a satisfactory response to an antidepressant medication should continue to receive a full therapeutic dose of that agent for at least 16–20 weeks after achieving and maintaining full remission (105, 225, 495).

Two clinical trials have examined the effects of continuation treatment following an acute course of ECT. In a randomized double-blind trial that included 84 individu-

als with major depressive disorder whose symptoms had remitted with ECT, the combination of nortriptyline (target steady-state level, 75–125 ng/mL) plus lithium (target steady-state level, 0.5–0.9 mEq/L) was associated with lower relapse rates over the 24-week trial (39%) than either nortriptyline alone (60%) or placebo (84%) (489). A subsequent trial found that continuation pharmacotherapy with lithium plus nortriptyline (N=94) was comparable in efficacy to continuation ECT (N=89) in maintaining remission (46.3% versus 46.1%) after a successful acute course of ECT (234). The group receiving medication reported a greater number of treatment-emergent side effects than the ECT group, but there were no differences in cognitive impairment reported between the treatment groups.

A few studies have examined treatment with psychotherapeutic interventions administered in the continuation phase. One study found that among patients who responded to acute treatment with cognitive therapy, those who continued this treatment over 2 years had lower relapse rates than those who did not have continuation treatment (493). Results from a series of studies (365, 367, 494) suggest that CBT may be an effective continuation treatment following antidepressant medication therapy for preventing relapse (364).

In a randomized controlled trial of cognitive group therapy as an adjunct to treatment as usual, Bockting et al. (497) studied 187 patients with recurrent major depressive disorder who were currently in remission. Cognitive group therapy was found to be effective in preventing relapse/recurrence, and this protective effect increased in concert with the number of previous depressive episodes.

Hollon et al. (68) assessed 104 patients with major depressive disorder who had responded to cognitive therapy, pharmacotherapy, or placebo and had remained improved during a 12-month continuation phase. Patients were withdrawn from treatment and followed for an additional 12 months. Cognitive therapy patients, who were allowed no more than three booster sessions over that year, had a lower rate of relapse (31%) than those withdrawn from medication (76%). They also exhibited no greater likelihood of depressive relapse than patients who continued pharmacotherapy (47%), suggesting possible lasting benefits of cognitive therapy.

## F. MAINTENANCE TREATMENT

The multicenter Prevention of Recurrent Episodes of Depression With Venlafaxine for Two Years (PREVENT) study was designed to evaluate patients with recurrent unipolar major depressive disorder randomly assigned to receive venlafaxine XR or fluoxetine. At the end of a 10-

week acute phase treatment, response rates were 79% for both venlafaxine XR and fluoxetine, with remission rates being 49% and 50%, respectively. In the 6-month continuation phase, response rates were 90% (venlafaxine XR) and 92% (fluoxetine), with rates of sustained remission of 52% and 58%, respectively. The cumulative probability of recurrence through the first 12 months of the maintenance phase treatment was 23.1% for venlafaxine and 42% for placebo. The cumulative probability of recurrence through the second 12 months of maintenance treatment was 8% in the venlafaxine XR group and 44.8% in the placebo group (226, 1159).

There have been fewer investigations of the effectiveness of psychotherapy in the maintenance phase. In one study, maintenance cognitive therapy delivered over 2 years was as effective as maintenance medication for recurrent major depressive disorder (514). Other reports indicate that IPT may effectively lengthen the interepisode interval for patients with recurrent depression who do not receive medication (289, 314, 513, 1056). Maintenance CBT as augmentation to medication prevented relapse relative to medication plus treatment as usual (368, 497, 1160).

Monthly maintenance psychotherapy with CBASP was more effective over a 1-year period than an assessment-only control condition for patients with chronic depression who had responded to acute treatment and remained improved in continuation therapy with CBASP (1161). A 6-year follow-up of patients treated with medication and continuation CBT found weakening but continuing ongoing benefits lasting as long as 3.5 years after completing CBT (1162). Research on cognitive therapy has explored the concept of an enduring benefit by acquiring persistent skills that reduce the risk of depressive relapse after treatment has ended (68, 1110).

The combined use of psychotherapy, such as CBT, cognitive therapy, or IPT, and pharmacotherapy in the maintenance phase has also been considered by investigators. Some results suggest that the combination of antidepressant medications plus psychotherapy may be additionally effective in preventing relapse over treatment with single modalities (314, 365, 506, 515, 516). However, in individuals older than age 70 years who received maintenance treatment with paroxetine and clinical management, interpersonal therapy and placebo, paroxetine and interpersonal therapy, or placebo and clinical management, the combination of paroxetine and interpersonal therapy offered no benefits over paroxetine and clinical management and each were superior to the other treatment conditions (729).

Electroconvulsive therapy has also been used in the maintenance phase. Evidence for its benefits comes largely from case reports and case series (1163–1168), al-

though a retrospective case-control study (1169) and a randomized prospective trial in older adults (730) demonstrated longer times to recurrence with use of maintenance ECT. The optimal frequency, duration, and method of

discontinuing maintenance ECT treatment have not been systematically studied, but typically ECT is tapered gradually with a return to more frequent treatments if depressive symptoms emerge (501).

## Part C

### FUTURE RESEARCH NEEDS

Notable progress has been made in our understanding of major depressive disorder and its treatment. However, there are still many unanswered questions about optimizing and individualizing treatment. The following areas require additional study.

To “personalize” care, and someday even prevent depression, we must understand factors that cause it. In the nearer term, science can focus on predictors of benefit and adverse effects of specific treatments. Potential causes of depression or moderators of treatment response may be found through genomics, proteomics, physiological markers, personality traits, personal experiences, co-occurring conditions, or clusters of specific depressive symptoms. Culture, race, and ethnicity merit study in shaping treatment selection and predicting response and side effects. Even if science were to offer perfect and personalized treatments for depression, patients must be able to gain access to care and adhere to recommended interventions. Thus, research must develop better ways to deliver treatment, optimizing effectiveness as well as efficacy. Research should also consider the cost-effectiveness of care and effects of treatment on functioning and quality of life. As the U.S. population ages and co-occurring illnesses become more common, studies are needed on ways to integrate care for depression with treatment for other psychiatric and medical problems. Most studies of major depressive disorder have examined the acute phase of treatment. More research is required on the continuation and maintenance phases. Questions abound on the persistence of biological and psychosocial treatment effects, when treatment may safely be discontinued, how recurrent depression differs from chronic varieties in the long term, and more.

The science of psychotherapy research continues to evolve. We need to understand how specific types of therapy compare to one another in the treatment of major depressive disorder and how to select a treatment for an individual. Research must disentangle nonspecific factors

from the unique features of a theoretically derived approach. It would be important to determine the components of specific psychotherapies that are responsible for efficacy, the patient-specific factors that moderate the efficacy of these therapies, the indications for using a particular psychotherapy, and the optimal duration and frequency of psychotherapy for particular patient subgroups, types of psychotherapy, or phases of depression treatment. Outcome measures of psychotherapy studies should not only examine acute symptom response but also whether psychotherapies have enduring, protective effects in averting relapse and recurrence of depression after treatment has ended. A manual-based model of psychodynamic therapy for depression (1170) may be helpful in the development of evidence concerning this approach. Strategies for sequencing psychotherapy in the overall treatment of major depressive disorder and for combining psychotherapy (either with pharmacotherapy or another psychotherapy) merit further study.

Much work remains to be done on medication intervention in depression. We should address the comparative efficacies, relative short- and long-term side effect profiles, and specific clinical indications of different antidepressant medications, augmentation strategies (e.g., second-generation antipsychotic medications, lithium, thyroid hormone) and combination treatment approaches (e.g., SSRIs and other moieties). This would include determining if particular treatments or combinations of treatments have differential efficacy in specific subgroups of patients with depression (e.g., patients with psychotic depression) and, for medications other than the TCAs, whether relationships exist between medication blood levels and therapeutic responses or side effects. Initial studies of monotherapy with second-generation antipsychotic agents appear promising, but additional study of the acute and long-term benefits and side effects is essential. The definition and implications of treatment-resistance for treatment selection also requires further clarification.