PRACTICE GUIDELINE FOR THE
Treatment of Patients With Major Depressive Disorder

Third Edition

WORK GROUP ON MAJOR DEPRESSIVE DISORDER

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Work Group on Major Depressive Disorder reports the following potentially competing interests for the period from May 2005 to May 2010:

Dr. Gelenberg reports consulting for Eli Lilly and Company, Pfizer, Best Practice, AstraZeneca, Wyeth, Cyberonics, Novartis, Forest Pharmaceuticals, Inc., GlaxoSmithKline, ZARS Pharma, Jazz Pharmaceuticals, Lundbeck, Takeda Pharmaceuticals North America, Inc., eResearch Technology, Dey Pharma, PGxHealth, and Myriad Genetics. He reports serving on speakers bureaus for Pfizer, GlaxoSmithKline, and Wyeth. He reports receiving research grant funding from Eli Lilly and Company, Pfizer, and GlaxoSmithKline. He reports stock ownership in Healthcare Technology Systems.

Dr. Freeman reports that she received research support from the Meadows Foundation, the National Institute for Mental Health, the U.S. Food and Drug Administration, the Institute for Mental Health Research, Forest, GlaxoSmithKline and Eli Lilly and Company (investigator-initiated trials), and Pronova Biocare (research materials). She received an honorarium for case-based peer-reviewed material for AstraZeneca's website. She reports consulting for Ther-Rx, Reliant, and Pamlab. She reports receiving an honorarium for speaking at an APA continuing medical education program that was sponsored by Forest and an honorarium for speaking at a continuing medication education program sponsored by KV Pharmaceuticals. She reports receiving an honorarium from Leerink Swann for participating in a focus group.

Dr. Markowitz reports consulting for Ono Pharmaceutical Co., Ltd. (2005). He reports receiving research support from Forest Pharmaceuticals, Inc. (2005). He reports receiving grant support from the National Institute of Mental Health (2005–2013), the National Alliance for Research in Schizophrenia and Depression (2005), and MINT: Mental Health Initiative (2005). He reports receiving royalties from American Psychiatric Publishing, Inc. (2005–2010), Basic Books (2005–2010), Elsevier (2005–2010), and Oxford University Press (2007–2010).

Dr. Rosenbaum reports attending advisory boards for Bristol-Myers Squibb, Cephalon, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, MedAvante, Neuronetics, Inc., Novartis, Orexigen Therapeutics, Inc., Organon BioSciences, Pfizer, Roche Diagnostics, Sanofi-aventis, Shire, and Wyeth. He reports consulting for Auspex Pharmaceuticals, Compellis Pharmaceuticals, EPIX Pharmaceuticals, Neuronetics, Inc., Organon BioSciences, Somaxon, and Supernus Pharmaceuticals, Inc. He reports receiving honoraria from lectureships for Boehringer Ingleheim, Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, and Schwartz Pharma. He was involved in the creation of the Massachusetts General Hospital Psychiatry Academy (MGH-PA) and has served as a panelist in four satellite broadcast programs. MGH-PA programs that have industry support are always multi-sponsored, and curriculum development by the Academy is independent of sponsorship; the curricula from January 2005 to March 2009 included sponsorship support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly and Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Medical Affairs LLC, Ortho-McNeil Pharmaceutical, sanofi-aventis, Shire, and Wyeth. He reports equity holdings in Compellis Pharmaceuticals, MedAvante, and Somaxon.

Dr. Thase reports that he provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Company, Forest Pharmaceuticals, Inc., Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Neuronetics, Inc., Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, L.L.C., Pfizer (formerly Wyeth-Ayerst Laboratories), Schering-Plough (formerly Organon), Shire U.S., Inc., Supernus Pharmaceuticals, Takeda (Lundbeck), and Transcept Pharmaceuticals. He was a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Pfizer (formerly Wyeth-Ayerst Laboratories), and Schering-Plough (formerly Organon). He received grant funding from Eli Lilly and Company, GlaxoSmithKline, the National Institute of Mental Health, the Agency for Healthcare Research and Quality, and Sepracor, Inc. He had equity holdings in MedAvante, Inc., and received royalty income from American Psychiatric Publishing, Inc., Guilford Publications, Herald House, Oxford University Press, and W.W. Norton and Company. His wife was employed as the group scientific director for Embryon (formerly Advogent), which does business with Bristol-Myers Squibb and Pfizer/Wyeth.

Dr. Trivedi reports that he was a consultant to or on speaker bureaus for Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals, Inc.), AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics, Inc., Eli Lilly and Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, L.P., Johnson & Johnson P.R.D., Meade-Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuti-

cals, Inc., Pfizer, Inc., Sepracor, Shire Development, Solvay Pharmaceuticals, VantagePoint, and Wyeth-Ayerst Laboratories. He received research support from the Agency for Healthcare Research and Quality, Corcept Therapeutics, Inc., Cyberonics, Inc., Merck, National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), Solvay Pharmaceuticals, Inc., and Targacept.

Dr. Van Rhoads reports no competing interests.

The Independent Review Panel, including Drs. Reus, DePaulo, Fawcett, Schneck, and Silbersweig, report no competing interests. The Independent Review Panel reviewed this guideline to assess potential biases and found no evidence of influence from the industry and other relationships of the Work Group disclosed above. The Steering Committee on Practice Guidelines also reviewed this guideline and found no evidence of influence from these relationships. The development process for this guideline, including the roles of the Work Group, Independent Review Panel, Steering Committee, APA Assembly, and APA Board of Trustees is described in "Overview of Guideline Development Process" on p. 11.

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CONTENTS

STATEMENT OF INTENT

The APA Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate recommendation regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data, the psychiatric evaluation, and the diagnostic and treatment options available. Such recommendations should incorporate the patient's personal and sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes.

This practice guideline was approved in May 2010 and published in October 2010.

OVERVIEW OF GUIDELINE DEVELOPMENT PROCESS

This practice guideline was developed under the direction of the Steering Committee on Practice Guidelines. The development process is detailed in a document entitled "APA Guideline Development Process," which is available from the APA Department of Quality Improvement and Psychiatric Services. Key features of this process include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable
- Development of evidence tables that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes
- Initial drafting of the guideline by a work group ("Work Group") that included psychiatrists with clinical and research expertise in major depressive disorder
- Production of multiple revised drafts with widespread review; 15 organizations and 71 individuals submitted comments.
- Review of the final draft by an Independent Review Panel of experts with no relationships with industry, who were charged to evaluate the guideline recommendations for bias from potential conflicts of interest.
- Approval by the APA Assembly and Board of Trustees.
- Planned revisions at regular intervals.

Development of this APA practice guideline was not financially supported by any commercial organization. In addition, the integrity of the guideline has been ensured by the following mechanisms:

1. Work Group members were selected on the basis of their expertise and integrity, and they agreed to disclose all potential conflicts of interest before and during their work on this guideline to the Steering Committee on Practice Guidelines and to each other. Employees of industry were not included on the group, and the group was balanced to include some persons with minimal industry relationships. As disclosed on pages 2–3, from initiation of work in 2005 to approval of the guideline in 2010, some members of the Work Group on Major Depressive Disorder had relationships with industry for which they received research grants or income from consulting or speaking related to treatments discussed in the guideline.
2. Iterative guideline drafts were broadly circulated to and reviewed by the Steering Committee, other experts, allied organizations, and the APA membership; reviewers were asked to disclose their own potential conflicts of interest relevant to evaluating their comments. Over 1,000 comments were received and were addressed by substantive revisions by the Work Group. Oversight of the draft review and revision process was provided by the chair and vice-chair of the Steering Committee and by the Medical Editor, none of whom had relationships with industry.
3. In response to a 2009 report by the Institute of Medicine (1), which advocated that professional organizations that develop and disseminate practice guidelines should adopt a new policy that members of guideline work groups have no significant relationships with industry, the following process was implemented: An independent review panel of experts ("Independent Review Panel") having no current relationships with industry also reviewed the guideline and was charged with identifying any possible bias. The Independent Review Panel found no evidence of bias.

The Work Group and the Steering Committee differed on how to rate the strength of recommendation for psychodynamic psychotherapy. Based on their review of the available empirical evidence on the use of psycho-

dynamic psychotherapy in individuals with major depressive disorder, the Work Group gave this treatment a level III rating, i.e., "may be recommended on the basis of individual circumstances." The Steering Committee gave a level II rating, "recommended with moderate clinical confidence," based on the long history of clinical experience with psychodynamic psychotherapy as well as findings from several studies of patients who had depressive symptoms but not major depressive disorder per se.

Relevant updates to the literature were identified through a MEDLINE literature search for articles published since the second edition of the guideline, published in 2000. For this edition of the guideline, literature was identified through a computerized search of MEDLINE, using PubMed, for the period from January 1999 to December 2006. Using the MeSH headings depression or depressive disorder, as well as the key words major depression, major depressive disorder, neurotic depression, neurotic depressive, dysthymia, dysthymic, dysthymic disorder, endogenous depression, endogenous depressive, melancholia, melancholic, psychotic depression, atypical depression, seasonal depression, postpartum depression, postpartum depressive symptoms, unipolar depression, unipolar depressive, or pseudodementia yielded 39,157 citations. An additional 8,272 citations were identified by using the key words depression or depressive in combination with the MeSH headings affective disorders or psychotic or the key words psychosis, psychotic, catatonic, catatonia, mood disorder, mood disorders, affective disorder, or affective disorders. These citations were limited to English language articles on human treatments using the MeSH headings central nervous system stimulants, hypnotics and sedatives, anticonvulsants, tranquilizing agents, electric stimulation therapy, electroconvulsive therapy, psychotherapy, antidepressive agents, and monoamine oxidase inhibitors or the key words antidepressant, antidepressants, antidepressive, antidepressive agents, antidepressive agents, second generation, antidepressive agents tricyclic, antidepressive agents, tricyclic, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, venlafaxine, duloxetine, mirtazapine, nefazodone, trazodone, imipramine, desipramine, nortriptyline, protriptyline, doxepin, trimipramine, amitriptyline, phenelzine, tranylcypromine, isocarboxazid, moclobemide, antipsychotic agents, testosterone, thyroid, tri iodothyronine, thyroxine, omega 3, *s* adenosyl methionine, *s* adenosylmethionine, St. John's wort, hypericum, selegiline, anticonvulsant, anticonvulsants, antipsychotic, antipsychotic agent, antianxiety, anti anxiety, benzodiazepine, benzodiazepines, zolpidem, sedative, sedatives, hypnotic, hypnotics, zaleplon, eszopiclone, valproate, valproic acid, divalproex, carbamazepine, oxcarbazepine, gabapentin, topiramate, lamotrigine, lithium, modafinil, methylphenidate, Adderall, amphetamine, amphetamines, dextroamphetamine, atomoxetine, electroconvulsive, vagal nerve stimulation, vagus nerve stimulation, VNS, rTMS, rapid transcranial magnetic, repetitive transcranial magnetic stimulation, magnetic stimulation, deep brain stimulation, psychotherapy, psychotherapeutic, psychotherapies, behavior therapy, behaviour therapy, cognitive therapy, cognitive behavior therapy, cognitive behavioral analysis system, cognitive behavioral therapy, cognitive behaviour therapy, cognitive behavioural therapy, psychoanalytic, interpersonal therapy, interpersonal psychotherapy, group therapy, family therapy, marital therapy, couples therapy, psychoanalysis, psychodynamic, aversive therapy, desensitization, exposure therapy, relaxation techniques, or progressive muscle relaxation. This yielded 13,506 abstracts, which were screened for relevance with a very modest threshold for inclusion, then reviewed by the Work Group.

The Psychoanalytic Electronic Publishing database (http://www.p-e-p.org) was also searched using the terms major depression or major depressive. This search yielded 112 references. The Cochrane databases were also searched for the key word depression, and 168 meta-analyses were identified. Additional, less formal, literature searches were conducted by APA staff and individual Work Group members and included references through May 2009. Sources of funding were considered when the Work Group reviewed the literature.

The broad scope of this guideline and the substantial evidence base resulted in some practical tradeoffs. One such tradeoff worth highlighting is the decision to build upon literature reviews of the first and second editions of the guideline, rather than re-do them. This decision is acknowledged to have resulted in an emphasis of study in this guideline on newer treatments, because the majority of studies about older treatments, including tricyclic antidepressants and monoamine oxidase inhibitors, were published in decades prior to 1999. Readers are advised that the reviews of this older literature are described in the previous editions of the guideline. The Work Group for this edition considered the previous editions during their evidence review, but for practical reasons, that effort is less well documented than the group's analysis of the newer literature. The treatment recommendations of this guideline, however, were developed to reflect the complete evidence base.

This document represents a synthesis of current scientific knowledge and rational clinical practice regarding the treatment of patients with major depressive disorder. It strives to be as free as possible of bias toward any theoretical approach to treatment. In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each

recommendation, the summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. Each rating of clinical confidence considers the strength of the available evidence. When evidence from randomized controlled trials and meta-analyses is limited, the level of confidence may also incorporate other clinical trials and case reports as well as clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition*, consists of three parts (Parts A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, "Treatment Recommendations," is published as a supplement to the *American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II is a guide to the formulation and implementation of a treatment plan for the individual patient. Section III, "Specific Clinical Features Influencing the Treatment Plan," discusses a range of clinical considerations that could alter the general recommendations discussed in Section I.

Part B, "Background Information and Review of Available Evidence," and Part C, "Future Research Needs," are not included in the *American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available in print format from American Psychiatric Publishing, Inc., and online through the American Psychiatric Association (http://www.psychiatryonline.com). Part B provides an overview of major depressive disorder, including general information on natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

To share feedback on this or other published APA practice guidelines, a form is available at http://mx.psych.org/survey/reviewform.cfm.

OFF-LABEL USE OF MEDICATIONS

Medications discussed in this practice guideline may not have an indication from the U.S. Food and Drug Administration for the disorder or condition for which they are recommended. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by the evidence provided in the APA practice guideline, other scientific literature, and clinical experience.

INTRODUCTION

This guideline summarizes the specific approaches to treatment of individuals with major depressive disorder. It presupposes that the psychiatrist has diagnosed major depressive disorder, according to the criteria defined in DSM-IV-TR, in an adult patient and has evaluated the patient to identify general medical conditions that may contribute to the disease process (e.g., hypothyroidism, pancreatic carcinoma) or complicate its treatment (e.g., cardiac disorders). The treatment recommendations that follow may also have some relevance for patients who have depressive symptoms on the basis of other syndromes, such as dysthymic disorder. Because many patients have co-occurring psychiatric disorders, including substance use disorders, the psychiatrist should also consider applicable treatment guidelines for these diagnoses. When patients experience depressive symptoms in the context of another disorder and do not meet the diagnostic criteria for major depressive disorder, the APA practice guideline pertaining to the primary diagnosis should be consulted. For patients found to have depressive symptoms within the context of bipolar disorder, the psychiatrist should refer to APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (2). Recommendations on the treatment of depressive disorders in children and adolescents can be found in the American Academy of Child and Adolescent Psychiatry's *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders* (3).

Part A

TREATMENT RECOMMENDATIONS

I. EXECUTIVE SUMMARY

A. CODING SYSTEM

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence:

[I] Recommended with substantial clinical confidence
[II] Recommended with moderate clinical confidence
[III] May be recommended on the basis of individual circumstances

B. SUMMARY OF RECOMMENDATIONS

1. Psychiatric management

Psychiatric management consists of a broad array of interventions and activities that psychiatrists should initiate and continue to provide to patients with major depressive disorder through all phases of treatment [I].

a. Establish and maintain a therapeutic alliance

In establishing and maintaining a therapeutic alliance, it is important to collaborate with the patient in decision making and attend to the patient's preferences and concerns about treatment [I]. Management of the therapeutic alliance should include awareness of transference and countertransference issues, even if these are not directly addressed in treatment [II]. Severe or persistent problems of poor alliance or nonadherence to treatment may be caused by the depressive symptoms themselves or may represent psychological conflicts or psychopathology for which psychotherapy should be considered [II].

b. Complete the psychiatric assessment

Patients should receive a thorough diagnostic assessment in order to establish the diagnosis of major depressive disorder, identify other psychiatric or general medical conditions that may require attention, and develop a comprehensive plan for treatment [I]. This evaluation generally includes a history of the present illness and current symptoms; a psychiatric history, including identification of past symptoms of mania, hypomania, or mixed episodes and responses to previous treatments; a general medical history; a personal history including information about psychological development and responses to life transitions and major life events; a social, occupational, and family history (including mood disorders and suicide); review of the patient's prescribed and over-the-counter medications; a review of systems; a mental status examination; a physical examination; and appropriate diagnostic tests as indicated to rule out possible general medical causes of depressive symptoms [I]. Assessment of substance use should evaluate past and current use of illicit drugs and other substances that may trigger or exacerbate depressive symptoms [I].

c. Evaluate the safety of the patient

A careful and ongoing evaluation of suicide risk is necessary for all patients with major depressive disorder [I]. Such an assessment includes specific inquiry about suicidal thoughts, intent, plans, means, and behaviors; identification of specific psychiatric symptoms (e.g., psychosis, severe anxiety, substance use) or general medical conditions that may increase the likelihood of acting on suicidal ideas; assessment of past and, particularly, recent suicidal behavior; delineation of current stressors and potential protective factors (e.g., positive reasons for living, strong social support); and identification of any family history of suicide or mental illness [I]. In addition to assessing suicide risk per se, it is important to assess the patient's level of self-care, hydration, and nutrition, each of which can be compromised by severe depressive symptoms [I]. As part of the assessment process, impulsivity and potential for risk to others should also be evaluated, including any history of violence or violent or homicidal ideas, plans, or intentions [I]. An evaluation of the impact of the depression on the patient's ability to care for dependents is an important component of the safety evaluation [I]. The patient's risk of harm to him- or herself and to others should also be monitored as treatment proceeds [I].

d. Establish the appropriate setting for treatment

The psychiatrist should determine the least restrictive setting for treatment that will be most likely not only to address the patient's safety, but also to promote improvement in the patient's condition [I]. The determination of an appropriate setting for treatment should include consideration of the patient's symptom severity, co-occurring psychiatric or general medical conditions, available support system, and level of functioning [I]. The determination of a treatment setting should also include consideration of the patient's ability to adequately care for him- or herself, to provide reliable feedback to the psychiatrist, and to cooperate with treatment of the major depressive disorder [I]. Measures such as hospitalization should be considered for patients who pose a serious threat of harm to themselves or others [I]. Patients who refuse inpatient treatment can be hospitalized involuntarily if their condition meets the criteria of the local jurisdiction for involuntary admission [I]. Admission to a hospital or, if available, an intensive day program, may also be indicated for severely ill patients who lack adequate social support outside of a hospital setting, who have complicating psychiatric or general medical conditions, or who have not responded adequately to outpatient treatment [I]. The optimal treatment setting and the patient's likelihood of benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment [I].

e. Evaluate functional impairment and quality of life

Major depressive disorder can alter functioning in numerous spheres of life including work, school, family, social relationships, leisure activities, or maintenance of health and hygiene. The psychiatrist should evaluate the patient's activity in each of these domains and determine the presence, type, severity, and chronicity of any dysfunction [I]. In developing a treatment plan, interventions should be aimed at maximizing the patient's level of functioning as well as helping the patient to set specific goals appropriate to his or her functional impairments and symptom severity [I].

f. Coordinate the patient's care with other clinicians

Many patients with major depressive disorder will be evaluated by or receive treatment from other health care professionals in addition to the psychiatrist. If more than one clinician is involved in providing the care, all treating clinicians should have sufficient ongoing contact with the patient and with each other to ensure that care is coordinated, relevant information is available to guide treatment decisions, and treatments are synchronized [I].

In ruling out general medical causes of depressive symptoms, it is important to ensure that a general medical evaluation has been done [I], either by the psychiatrist or by another health care professional. Extensive or specialized testing for general medical causes of depressive symptoms may be conducted based on individual characteristics of the patient [III].

g. Monitor the patient's psychiatric status

The patient's response to treatment should be carefully monitored [I]. Continued monitoring of co-occurring psychiatric and/or medical conditions is also essential to developing and refining a treatment plan for an individual patient [I].

h. Integrate measurements into psychiatric management

Tailoring the treatment plan to match the needs of the particular patient requires a careful and systematic assessment of the type, frequency, and magnitude of psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment [I]. Such assessments can be facilitated by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation [II].

i. Enhance treatment adherence

The psychiatrist should assess and acknowledge potential barriers to treatment adherence (e.g., lack of motivation or excessive pessimism due to depression; side effects of treatment; problems in the therapeutic relationship; logistical, economic, or cultural barriers to treatment) and collaborate with the patient (and if possible, the family) to minimize the impact of these potential barriers [I]. In addition, the psychiatrist should encourage patients to articulate any fears or concerns about treatment or its side effects [I]. Patients should be given a realistic notion of what can be expected during the different phases of treatment, including the likely time course of symptom response and the importance of adherence for successful treatment and prophylaxis [I].

j. Provide education to the patient and the family

Education about the symptoms and treatment of major depressive disorder should be provided in language that is readily understandable to the patient [I]. With the patient's permission, family members and others involved in the patient's day-to-day life may also benefit from education about the illness, its effects on functioning (including family and other interpersonal relationships), and its treatment [I]. Common misperceptions about antidepressants (e.g., they are addictive) should be clarified [I]. In addition, education about major depressive disorder should address the need for a full acute course of treatment, the risk of relapse, the early recognition of recurrent symptoms, and the need to seek treatment as early as possible to reduce the risk

of complications or a full-blown episode of major depression [I]. Patients should also be told about the need to taper antidepressants, rather than discontinuing them precipitously, to minimize the risk of withdrawal symptoms or symptom recurrence [I]. Patient education also includes general promotion of healthy behaviors such as exercise, good sleep hygiene, good nutrition, and decreased use of tobacco, alcohol, and other potentially deleterious substances [I]. Educational tools such as books, pamphlets, and trusted web sites can augment the face-to-face education provided by the clinician [I].

2. Acute phase

a. Choice of an initial treatment modality

Treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [I]. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy, as described in the sections that follow. Selection of an initial treatment modality should be influenced by clinical features (e.g., severity of symptoms, presence of co-occurring disorders or psychosocial stressors) as well as other factors (e.g., patient preference, prior treatment experiences) [I]. Any treatment should be integrated with psychiatric management and any other treatments being provided for other diagnoses [I].

1. Pharmacotherapy

An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [I] and definitely should be provided for those with severe major depressive disorder unless ECT is planned [I]. Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [I]. For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal [I]. In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments [I], given the necessity for dietary restrictions with these medications and the potential for deleterious drug-drug interactions. In patients who prefer complementary and alternative therapies, *S*-adenosyl methionine (SAMe) [III] or St. John's wort [III] might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort [I].

Once an antidepressant medication has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting, and the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [I]. During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy, identify the emergence of side effects (e.g., gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects), and assess patient safety [I]. The frequency of patient monitoring should be determined based upon the patient's symptom severity (including suicidal ideas), co-occurring disorders (including general medical conditions), cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [II]. If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [I].

2. Other somatic therapies

ECT is recommended as a treatment of choice for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly in those who have significant functional impairment or have not responded to numerous medication trials [I]. ECT is also recommended for individuals with major depressive disorder who have associated psychotic or catatonic features [I], for those with an urgent need for response (e.g., patients who are suicidal or nutritionally compromised due to refusal of food or fluids) [I], and for those who prefer ECT or have had a previous positive response to ECT [II].

Bright light therapy might be used to treat seasonal affective disorder as well as nonseasonal depression [III].

3. Psychotherapy

Use of a depression-focused psychotherapy alone is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [I], with clinical evidence supporting the use of cognitive-behavioral therapy (CBT) [I], interpersonal psychotherapy [I], psy-

chodynamic therapy [II], and problem-solving therapy [III] in individual [I] and in group [III] formats. Factors that may suggest the use of psychotherapeutic interventions include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, a co-occurring axis II disorder, treatment availability, or—most important—patient preference [II]. In women who are pregnant, wish to become pregnant, or are breastfeeding, a depression-focused psychotherapy alone is recommended [II] and depending on the severity of symptoms, should be considered as an initial option [I]. Considerations in the choice of a specific type of psychotherapy include the goals of treatment (in addition to resolving major depressive symptoms), prior positive response to a specific type of psychotherapy, patient preference, and the availability of clinicians skilled in the specific psychotherapeutic approach [II]. As with patients who are receiving pharmacotherapy, patients receiving psychotherapy should be carefully and systematically monitored on a regular basis to assess their response to treatment and assess patient safety [I]. When determining the frequency of psychotherapy sessions for an individual patient, the psychiatrist should consider multiple factors, including the specific type and goals of psychotherapy, symptom severity (including suicidal ideas), co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency of visits necessary to create and maintain a therapeutic relationship, ensure treatment adherence, and monitor and address depressive symptoms and suicide risk [II]. Marital and family problems are common in the course of major depressive disorder, and such problems should be identified and addressed, using marital or family therapy when indicated [II].

4. Psychotherapy plus antidepressant medication

The combination of psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder [I]. In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder [II]. In general, when choosing an antidepressant or psychotherapeutic approach for combination treatment, the same issues should be considered as when selecting a medication or psychotherapy for use alone [I].

b. Assessing the adequacy of treatment response

In assessing the adequacy of a therapeutic intervention, it is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose [I]. Onset of benefit from psychotherapy tends to be a bit more gradual than that from medication, but no treatment should continue unmodified if there has been no symptomatic improvement after 1 month [I]. Generally, 4–8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention [II].

c. Strategies to address nonresponse

For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely [I], as an incomplete response to treatment is often associated with poor functional outcomes. If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [I]. It is also important to assess the quality of the therapeutic alliance and treatment adherence [I]. For patients in psychotherapy, additional factors to be assessed include the frequency of sessions and whether the specific approach to psychotherapy is adequately addressing the patient's needs [I]. If medications are prescribed, the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. With some TCAs, a drug blood level can help determine if additional dose adjustments are required [I].

After an additional 4–8 weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan [I]. Consultation should also be considered [II].

A number of strategies are available when a change in the treatment plan seems necessary. For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a tricyclic antidepressant [TCA]) [II]. For patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmaco-

logical class, or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or a second-generation antipsychotic [II]. Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant [III], omega-3 fatty acids [III], folate [III], or a psychostimulant medication [III], including modafinil [III]. If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotic medications [III], including buspirone, benzodiazepines, and selective γ-aminobutyric acid (GABA) agonist hypnotics (e.g., zolpidem, eszopiclone). For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II]. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III].

For patients treated with psychotherapy, consideration should be given to increasing the intensity of treatment or changing the type of therapy [II]. If psychotherapy is used alone, the possible need for medications in addition to or in lieu of psychotherapy should be assessed [I]. Patients who have a history of poor treatment adherence or incomplete response to adequate trials of single treatment modalities may benefit from combined treatment with medication and a depression-focused psychotherapy [II].

3. Continuation phase

During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse [I]. Systematic assessment of symptoms, side effects, adherence, and functional status is essential [I] and may be facilitated through the use of clinician- and/or patient-administered rating scales [II]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended [I], with the best evidence available for CBT.

Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline. Alternatively, patients who have responded to an acute course of ECT may be given continuation ECT, particularly if medication or psychotherapy has been ineffective in maintaining remission [II].

4. Maintenance phase

In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior major depressive episodes or who have chronic major depressive disorder should proceed to the maintenance phase of treatment after completing the continuation phase [I]. Maintenance therapy should also be considered for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes (including factors such as psychosis or suicide risk), the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. Such factors also contribute to decisions about the duration of the maintenance phase [II]. For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely [I].

During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II]. If a depression-focused psychotherapy has been used during the acute and continuation phases of treatment, maintenance treatment should be considered, with a reduced frequency of sessions [II]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality [III].

Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase [I]. Use of standardized measurement aids in the early detection of recurrent symptoms [II].

5. Discontinuation of treatment

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks [I]. To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II] when discontinuing antidepressants or reducing antidepressant doses. Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms [I]. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur [I].

For patients receiving psychotherapy, it is important to raise the issue of treatment discontinuation well in advance of the final session [I], although the exact process by which this occurs will vary with the type of therapy.

6. Clinical factors influencing treatment

a. Psychiatric factors

For suicidal patients, psychiatrists should consider an increased intensity of treatment, including hospitalization when warranted [I] and/or combined treatment with pharmacotherapy and psychotherapy [II]. Factors to consider in determining the nature and intensity of treatment include (but are not limited to) the nature of the doctor-patient alliance, the availability and adequacy of social supports, access to and lethality of suicide means, the presence of a co-occurring substance use disorder, and past and family history of suicidal behavior [I].

For patients who exhibit psychotic symptoms during an episode of major depressive disorder, treatment should include a combination of antipsychotic and antidepressant medications or ECT [I]. When patients exhibit cognitive dysfunction during a major depressive episode, they may have an increased likelihood of future dementia, making it important to assess cognition in a systematic fashion over the course of treatment [I].

Catatonic features that occur as part of a major depressive episode should be treated with a benzodiazepine [I] or barbiturate [II], typically in conjunction with an antidepressant [II]. If catatonic symptoms persist, ECT is recommended [I]. To reduce the likelihood of general medical complications, patients with catatonia may also require supportive medical interventions, such as hydration, nutritional support, prophylaxis against deep vein thrombosis, turning to reduce risks of decubitus ulcers, and passive range of motion to reduce risk of contractures [I]. If antipsychotic medication is needed, it is important to monitor for signs of neuroleptic malignant syndrome, to which patients with catatonia may have a heightened sensitivity [II].

When patients with a major depressive disorder also have a co-occurring psychiatric illness, the clinician should address each disorder as part of the treatment plan [I]. Benzodiazepines may be used adjunctively in individuals with major depressive disorder and co-occurring anxiety [II], although these agents do not treat depressive symptoms, and careful selection and monitoring is needed in individuals with co-occurring substance use disorders [I].

In patients who smoke, bupropion [I] or nortriptyline [II] may be options to simultaneously treat depression and assist with smoking cessation. When possible, a period of substance abstinence can help determine whether the depressive episode is related to substance intoxication or withdrawal [II]. Factors that suggest a need for antidepressant treatment soon after cessation of substance use include a family history of major depressive disorder and a history of major depressive disorder preceding the onset of the substance use disorder or during periods of sobriety [II].

For patients who have a personality disorder as well as major depressive disorder, psychiatrists should institute treatment for the major depressive disorder [I] and consider psychotherapeutic and adjunctive pharmacotherapeutic treatment for personality disorder symptoms [II].

b. Demographic and psychosocial factors

Several aspects of assessment and treatment differ between women and men. Because the symptoms of some women may fluctuate with gonadal hormone levels, the evaluation should include a detailed assessment of mood changes across the reproductive life history (e.g., menstruation, pregnancy, birth control including oral contraception use, abortions, menopause) [I]. When prescribing medications to women who are taking oral contraceptives, the potential effects of drug-drug interactions must be considered [I]. For women in the perimenopausal period, SSRI and SNRI antidepressants are useful in ameliorating depression as well as in reducing somatic symptoms such as hot flashes [II]. Both men and women who are taking antidepressants should be asked whether sexual side effects are occurring with these medications [I]. Men for whom trazodone is prescribed should be warned of the risk of priapism [I].

The treatment of major depressive disorder in women who are pregnant or planning to become pregnant requires a careful consideration of the benefits and risks of

available treatment options for the patient and the fetus [I]. For women who are currently receiving treatment for depression, a pregnancy should be planned, whenever possible, in consultation with the treating psychiatrist, who may wish to consult with a specialist in perinatal psychiatry [I]. In women who are pregnant, planning to become pregnant, or breast-feeding, depression-focused psychotherapy alone is recommended [II] and should always be considered as an initial option, particularly for mild to moderate depression, for patients who prefer psychotherapy, or for those with a prior positive response to psychotherapy [I]. Antidepressant medication should be considered for pregnant women who have moderate to severe major depressive disorder as well as for those who are in remission from major depressive disorder, are receiving maintenance medication, and are deemed to be at high risk for a recurrence if the medication is discontinued [II]. When antidepressants are prescribed to a pregnant woman, changes in pharmacokinetics during pregnancy may require adjustments in medication doses [I]. Electroconvulsive therapy may be considered for the treatment of depression during pregnancy in patients who have psychotic or catatonic features, whose symptoms are severe or have not responded to medications, or who prefer treatment with ECT [II]. When a woman decides to nurse, the potential benefits of antidepressant medications for the mother should be balanced against the potential risks to the newborn from receiving antidepressant in the mother's milk [I]. For women who are depressed during the postpartum period, it is important to evaluate for the presence of suicidal ideas, homicidal ideas, and psychotic symptoms [I]. The evaluation should also assess parenting skills for the newborn and for other children in the patient's care [I].

In individuals with late-life depression, identification of co-occurring general medical conditions is essential, as these disorders may mimic depression or affect choice or dosing of medications [I]. Older individuals may also be particularly sensitive to medication side effects (e.g., hypotension, anticholinergic effects) and require adjustment of medication doses for hepatic or renal dysfunction [I]. In other respects, treatment for depression should parallel that used in younger age groups [I].

The assessment and treatment of major depressive disorder should consider the impact of language barriers, as well as cultural variables that may influence symptom presentation, treatment preferences, and the degree to which psychiatric illness is stigmatized [I]. When antidepressants are prescribed, the psychiatrist should recognize that ethnic groups may differ in their metabolism and response to medications [II].

Issues relating to the family situation and family history, including mood disorders and suicide, can also affect treatment planning and are an important element of the initial evaluation [I]. A family history of bipolar disorder or acute psychosis suggests a need for increased attention to possible signs of bipolar illness in the patient (e.g., with antidepressant treatment) [I]. A family history of recurrent major depressive disorder increases the likelihood of recurrent episodes in the patient and supports a need for maintenance treatment [II]. Family history of a response to a particular antidepressant may sometimes help in choosing a specific antidepressant for the patient [III]. Because problems within the family may become an ongoing stressor that hampers the patient's response to treatment, and because depression in a family is a major stress in itself, such factors should be identified and strong consideration given to educating the family about the nature of the illness, enlisting the family's support, and providing family therapy, when indicated [II].

For patients who have experienced a recent bereavement, psychotherapy or antidepressant treatment should be used when the reaction to a loss is particularly prolonged or accompanied by significant psychopathology and functional impairment [I]. Support groups may be helpful for some bereaved individuals [III].

c. Co-occurring general medical conditions

In patients with major depressive disorder, it is important to recognize and address the potential interplay between major depressive disorder and any co-occurring general medical conditions [I]. Communication with other clinicians who are providing treatment for general medical conditions is recommended [I]. The clinical assessment should include identifying any potential interactions between medications used to treat depression and those used to treat general medical conditions [I]. Assessment of pain is also important as it can contribute to and co-occur with depression [I]. In addition, the psychiatrist should consider the effects of prescribed psychotropic medications on the patient's general medical conditions, as well as the effects of interventions for such disorders on the patient's psychiatric condition [I].

In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., electrocardiogram [ECG] with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [I]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individ-

uals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [I]. Some antidepressant drugs (e.g., bupropion, clomipramine, maprotiline) reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [II]. In individuals with Parkinson's disease, the choice of an antidepressant should consider that serotonergic agents may worsen symptoms of the disease [II], that bupropion has potential dopamine agonist effects (benefitting symptoms of Parkinson's disease but potentially worsening psychosis) [II], and that selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [I]. In treating the depressive syndrome that commonly occurs following a stroke, consideration should be given to the potential for interactions between antidepressants and anticoagulating (including antiplatelet) medications [I]. Given the health risks associated with obesity and the tendency of some antidepressant medications to contribute to weight gain, longitudinal monitoring of weight (either by direct measurement or patient report) is recommended [I], as well as calculation of body mass index (BMI) [II]. If significant increases are noted in the patient's weight or BMI, the clinician and patient should discuss potential approaches to weight control such as diet, exercise, change in medication, nutrition consultation, or collaboration with the patient's primary care physician [I]. In patients who have undergone bariatric surgery to treat obesity, adjustment of medication formulations or doses may be required because of altered medication absorption [I]. For diabetic patients, it is useful to collaborate with the patient's primary care physician in monitoring diabetic control when initiating antidepressant therapy or making significant dosing adjustments [II]. Clinicians should be alert to the possibility of sleep apnea in patients with depression, particularly those who present with daytime sleepiness, fatigue, or treatment-resistant symptoms [II]. In patients with known sleep apnea, treatment choice should consider the sedative side effects of medication, with minimally sedating options chosen whenever possible [I]. Given the significant numbers of individuals with unrecognized human immunodeficiency virus (HIV) infection and the availability of effective treatment, consideration should be given to HIV risk assessment and screening [I]. For patients with HIV infection who are receiving antiretroviral therapy, the potential for drug-drug interactions needs to be assessed before initiating any psychotropic medications [I]. Patients who are being treated with antiretroviral medications should be cautioned about drug-drug interactions with St. John's wort that can reduce the effectiveness of HIV treatments [I]. In patients with hepatitis C infection, interferon can exacerbate depressive symptoms, making it important to monitor patients carefully for worsening depressive symptoms during the course of interferon treatment [I]. Because tamoxifen requires active 2D6 enzyme function to be clinically efficacious, patients who receive tamoxifen for breast cancer or other indications should generally be treated with an antidepressant (e.g., citalopram, escitalopram, venlafaxine, desvenlafaxine) that has minimal effect on metabolism through the cytochrome P450 2D6 isoenzyme [I]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [II]. When ECT is used to treat major depressive disorder in an individual with a co-occurring general medical condition, the evaluation should identify conditions that could require modifications in ECT technique (e.g., cardiac conditions, hypertension, central nervous system lesions) [I]; these should be addressed insofar as possible and discussed with the patient as part of the informed consent process [I].

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

A. PSYCHIATRIC MANAGEMENT

For all patients with major depressive disorder, psychiatric management includes a broad array of possible interventions and activities. Essential components include educating the patient and when appropriate the family about depression, discussing treatment options and interventions, and enhancing adherence to treatment. Developing a successful plan of treatment for individuals with major depressive disorder is also promoted by an initial, thorough assessment of the patient. In addition, the psychiatrist must determine the treatment setting that will be most likely to enhance the patient's safety as well as promote improvement in the patient's condition. These elements of psychiatric management are described in more detail below.

1. Establish and maintain a therapeutic alliance

A psychiatric assessment begins with establishing therapeutic rapport and developing an alliance with the patient, regardless of the treatment modalities ultimately selected. The alliance itself may be the primary active therapeutic agent even for patients who receive monotherapy with medication (4). To establish and maintain a therapeutic alliance, it is important for the psychiatrist to be sensitive to the patient's concerns. By virtue of their depressed state, patients often view themselves in a negative light. They may feel unworthy of help, embarrassed or ashamed of having an illness, guilty about placing burdens on family members or the clinician, and distant or alienated from others. Individuals may also have a negative view of prior treatment experiences or have misconceptions about psychiatric treatment, which can color the therapeutic relationship. Such issues require open discussion to educate the patient about the goals and framework of treatment and to provide an empathic and trusting environment in which the patient feels comfortable expressing his or her self-doubts, fears, and other concerns. Cultural and religious factors may influence the patient's view of the depressive illness, his or her receptiveness to psychiatric treatment, and his or her preference of treatment modalities (5–7). Establishing a therapeutic alliance with a clinician of a different background may present additional challenges for some patients. Management of the therapeutic alliance should also include awareness of transference and countertransference issues, even if these are not directly addressed in treatment.

Because patients frequently have strong preferences about treatment options, the psychiatrist should identify the patient's wishes for treatment and collaborate with the patient in choosing among effective treatments. In addition, treatment adherence can be enhanced by the delivery of patient-centered care and by a strong treatment alliance with the psychiatrist. Severe or persistent problems of poor alliance or nonadherence to treatment may be caused by the depressive symptoms themselves. They may also represent psychological conflicts or a psychopathological condition for which psychotherapy should be considered.

If possible and appropriate, the family should be included in discussions about the patient's illness and plans for treatment. When family members are involved, they can also be encouraged to play a helpful role in improving the patient's adherence to treatment and supporting the therapeutic alliance.

2. Complete the psychiatric assessment

Patients with symptoms of depression should receive a thorough biopsychosocial assessment, both to determine whether a diagnosis of major depressive disorder is warranted and to identify the presence of other psychiatric or general medical conditions. The general principles and components of a complete psychiatric evaluation have been outlined in APA's *Practice Guideline for Psychiatric Evaluation of Adults, Second Edition* (8). The evaluation includes a history of the present illness and current symptoms, including vegetative symptoms and symptoms of mania or psychosis, as well as a psychiatric history that particularly notes current treatments, responses to previous treatments, past hospitalizations or suicide attempts, and the presence of co-occurring psychiatric disorders. Assessing the severity of the specific symptoms of depression may be aided by the use of standardized clinician- or patient-administered rating scales such as those described in Section II.A.8.

Many individuals with depression attempt to alleviate symptoms through the use of alternative or complementary treatments, over-the-counter or prescription medications or dietary regimens, or through use of caffeine, tobacco, alcohol, or other substances, which may precipitate or exacerbate depressive symptoms. Consequently, each of these factors should be carefully assessed. The personal history will include an assessment of psychological development; a sexual history, including history of sexual abuse or assault; identification of early life trauma, including physical, sexual, or emotional abuse or neglect; determination of responses to life transitions, major life events, or significant traumas; a social history; and an occupational history, including history of military service. Co-occurring general medical conditions are common and can influence the diagnosis of major depressive disorder as well as choices of treatment. Thus, a general medical history is essential, along with a review of the patient's current medications; a review of systems, including assessment for pain; and any indicated diagnostic tests or physical examinations. The latter may be done by the psychiatrist or by another physician or medically trained clinician. A mental status examination is crucial in identifying signs of depression, associated psychosis, cognitive deficits, and factors influencing suicide risk (e.g., suicidal ideas, anxiety), as well as in identifying co-occurring psychiatric disorders. Because major depressive disorder is associated with functional impairment, the presence, type, and severity of the dysfunction should be evaluated. Impairments can include deficits in interpersonal relationships and family functioning, work performance, maintenance of health and hygiene, and deficits in quality of life. Whenever feasible, assessment should also include input from family members in order to determine the impact of the patient's condition on his or her family. Family members and significant others can also report key elements of the patient's history or

recent status that the patient may minimize or be unable to recall or report accurately. In addition, family functioning may affect the outcome of the patient's depressive illness (9, 10).

A family history is also important to obtain and involves the collection of the family pedigree including parents, grandparents, and number and sex of siblings and children. For patients with children at home, information on their symptom state may be useful because of the high possibility of psychiatric problems in the offspring of a depressed parent (11, 12). Such problems may require intervention or may be an added stressor for the patient. The family history includes history of depression or other mood disorders, substance use disorders, psychosis, suicide, and unusual behaviors in the patient's relatives along with any associated impairments. Because family history is a potent and consistent risk factor for mental disorders, formulating diagnosis and treatment decisions for the patient can be aided by knowing the age of onset and severity of psychiatric symptoms in the patient's family, as well as relatives' psychiatric treatment history, especially the tolerability and effectiveness of those treatments.

In establishing a diagnosis of major depressive disorder as part of the initial assessment, other differential diagnostic possibilities are important to consider. An initial consideration in the differential diagnosis is mood disorder due to a general medical condition. Specific medical conditions that are important to consider and that may be associated with a major depressive episode include neurological conditions (e.g., stroke, Parkinson's disease, dementia, multiple sclerosis), thyroid disorders, metabolic conditions (e.g., hypercalcemia), malignancy, and infectious diseases (13–15). Depressive symptoms that would otherwise be diagnosable as major depressive disorder are diagnosed instead as a mood disorder due to a general medical condition if the mood disturbance is judged to be the direct physiological consequence of a specific general medical condition. Similarly, medications used to treat general medical conditions may induce depressive syndromes. Such medications include transplant anti-rejection agents, chemotherapy agents, interferon, steroids, some antibiotics, and others. Depression caused by medications is classified in the DSM-IV-TR as other (or unknown) substance-induced mood disorder (DSM-IV-TR code 292.84) (16).

Psychosocial stressors and other antecedent events, and their possible contribution to the generation of depressive symptoms, should be explored in the course of a psychiatric assessment. Depressive symptoms are a common response to psychosocial stressors, particularly bereavement. Symptoms characteristic of a major depressive episode may arise after a significant loss; however, the diagnosis of major depressive disorder is generally not given unless depressive symptoms are still present 2 months after the loss, are particularly severe, or are uncharacteristic of or unrelated to bereavement, such as persistent suicidal ideation or morbid preoccupation with worthlessness or guilt (16). Following a stressor, depressive symptoms that do not reach sufficient number or severity to be classified as a major depressive episode may be better described as an adjustment disorder. Despite the possible presence of antecedent stressors, psychiatrists should not dismiss potentially disabling depressive symptoms as "normal," thereby depriving patients of needed therapeutic attention.

A thorough assessment of depression also includes the evaluation of psychotic symptoms. Major depressive disorder may be associated with mood-congruent and mood-incongruent hallucinations and delusions. Depressed patients may not initially present with psychotic symptoms, and patients may wish to hide shaming or distressing thoughts. Therefore, psychiatrists should carefully query patients about such symptoms in order to provide appropriate treatments for them (see Section III.A.2.a). Identifying the presence of atypical, melancholic, or catatonic features of depression is also important, as such features may influence the choice of treatments (see Sections III.A.2.b, III.A.2.c, and III.A.2.d). Considering that major depressive episodes are common in the course of bipolar I disorder and that recurrent major depressive episodes are characteristic of bipolar II disorder (17), it is important to consider bipolar disorders as part of the differential diagnosis of major depressive disorder. This distinction is especially important because the treatments for bipolar disorders often differ from those for major depressive disorder.

All patients who present for treatment for a major depressive episode should be screened for a past history of manic or hypomanic episodes and for past adverse reactions to antidepressants that might be consistent with a "switch" into hypomania or mania. Screening instruments for manic and hypomanic episodes include the Mood Disorders Questionnaire (18) and the Screening Assessment of Depression–Polarity, which includes three easily administered dichotomous questions (19). However, since patients are often unaware of prior hypomanic or manic episodes, even when questioned carefully, collateral sources of information, such as family members living with the patient, may be crucial in uncovering such episodes. Clinical assessment should also include whether or not the patient is experiencing a mixed episode, which is characterized by symptoms of both a major depressive episode and a manic episode that occur nearly every day for at least 1 week.

It is also important to consider the frequency and chronicity of prior episodes of major depressive disorder.

Chronic forms of depression—such as dysthymic disorder, "double depression" (dysthymic disorder and major depressive disorder), and major depressive disorder with the "chronic" specifier—are all depressions with a duration of at least 2 years. In clinical studies, chronic depression has a lower response rate than nonchronic depression, but because the placebo-response rate is also lower, the relative clinical benefit is comparable. The onset of benefit in chronic depression appears more gradual than in nonchronic depression. However, despite a smaller response rate and slower response, it is important to recognize that chronic depression is not treatment refractory (20). Unfortunately, however, in many patients, chronic depression remains undiagnosed or, if diagnosed, undertreated (21).

The presence of a family history of a mood disorder should also be determined. Family histories of major depressive disorder and bipolar disorder are common in those with major depressive disorder, but a family history of bipolar disorder may indicate increased risk of bipolar disorder in the patient. A family history of suicide is relevant in determining a patient's suicide risk (22) and may also signal the presence of an unrecognized mood disorder in a relative.

3. Evaluate the safety of the patient

Addressing safety concerns may take precedence over establishing a full differential diagnosis or completing the psychiatric assessment. Because of the increased rates of suicide in depressed patients (22–24), a thorough and ongoing evaluation of the patient's suicide risk is essential. Some components of an evaluation for suicidal risk are summarized in Table 1. The psychiatrist should evaluate the presence of suicidal ideation and behaviors, the extent to which the patient has made plans for or begun to prepare for suicide, the availability and lethality of the means for suicide, and the degree to which the patient intends to act on suicidal plans. A complete assessment also includes clinical factors that may increase the likelihood of a patient's acting on suicidal ideation, including a history of prior suicide attempts and the presence of psychotic symptoms, severe anxiety, panic attacks, impulsivity, and substance use. Patients should also be asked about a family history of suicide and recent exposure to suicide or suicide attempts by others. A suicide risk assessment should be individualized to the particular circumstances of the patient by including an evaluation of the patient's strengths, motivation to seek help, social support systems, and physical health.

Despite the best efforts of the psychiatrist, some patients may engage in self-harm (22). Even with careful assessments of suicide risk, the ability to predict suicidal behavior is poor, with many false positives (i.e., patients who appear more likely to make attempts or die by suicide

TABLE 1. Factors to Consider in Assessing Suicide Risk

Lifetime history, nature, seriousness, and number of previous attempts and aborted attempts
Presence, history, and lethality of suicidal ideation, intent, or plans
Access to means for suicide and the lethality of those means, such as access to a firearm
Presence of hopelessness, psychic pain, decreased self-esteem, narcissistic vulnerability
Presence of severe anxiety, panic attacks, agitation, impulsivity
Presence and history of aggression and violence
Nature of cognition, such as loss of executive function, thought constriction (tunnel vision), polarized thinking, closed-mindedness, poor coping and problem-solving skills
Presence of psychotic symptoms, such as command hallucinations or poor reality testing
Presence of alcohol or other substance use
Presence of major psychiatric disorders, such as major depressive disorder, bipolar disorder, schizophrenia, anorexia nervosa, alcohol use disorder, other substance use disorders, cluster B personality disorders
Recent psychiatric hospitalization
Presence of disabling medical illness, especially with poor prognosis, such as chronic pain, brain and spinal cord injury, malignant neoplasm, HIV or acquired immunodeficiency syndrome (AIDS), Huntington's disease, chronic hemodialysis-treated renal failure, chronic obstructive pulmonary disease
Demographic features, such as age, race, marital status, sexual orientation
Presence of acute or chronic psychosocial stressors, which may include actual or perceived interpersonal losses, financial difficulties or changes in socioeconomic status, family discord, domestic partner violence, and past or current sexual or physical abuse or neglect
Absence of psychosocial support, such as poor relationships with family, unemployment, living alone, unstable or poor therapeutic relationship, recent loss of a relationship
History of childhood traumas, particularly sexual and physical abuse
Family history of or recent exposure to suicide
Absence of protective factors, such as children in the home, sense of responsibility to family, pregnancy, life satisfaction, cultural beliefs, or religiosity

Source: Adapted from APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (22).

but who do not) as well as false negatives (i.e., patients who appear less likely to make attempts or die by suicide but who do). The assessment of suicide risk is complicated by the fact that suicidal individuals often conceal their thoughts and plans or act impulsively on short-lived suicidal thoughts, making their response to direct questions an unreliable predictor of dangerousness to self. For this reason, in addition to using direct questioning, the psychiatrist should also obtain information through observation and collateral history whenever possible (22, 25).

The risk of suicide should also be monitored as treatment proceeds, since variations in depressive symptoms may be associated with fluctuations in suicide risk. In youth and young adults, increases in suicidal thoughts and attempts have been reported early in the course of treatment with antidepressants, although no increases in mortality rates were seen in clinical trials (26). Family members can provide information that increases the likelihood of early detection of harmful behaviors. It is also useful to convey the expectation that family members will call the psychiatrist if concerns for safety emerge (27). For information about how suicidal ideation or behaviors affect the treatment plan, see Section III.A.1.a.

Although the greatest risk surrounding depression involves the patient's health, a rare but also potentially disastrous outcome of depression is violence toward others, including homicide (28, 29). Psychosis, substance abuse, impulsivity, and a history of aggression increase this risk (30–32). Psychiatrists accordingly should assess not only suicidal risk but also history of violence, homicidal ideation, and plans of violence toward others. Additional assessment may be necessary under specific circumstances. For example, it is important to assess the impact of parental depression (including peripartum depression) on children in the home, with specific attention given to the parent's vulnerability to neglect or harm the children (33). Whenever suicidal or violent ideas are expressed or suspected, careful documentation of the decision-making process is essential. In addition, patients who exhibit suicidal or violent ideas or intent require close monitoring.

4. Establish the appropriate setting for treatment

Treatment settings for patients with major depressive disorder include a continuum of possible levels of care, from involuntary hospitalizations to partial hospital programs, skilled nursing homes, and in-home care. In general, patients should be treated in the least restrictive setting that is most likely to prove safe and effective. The psychiatrist should choose an appropriate site of treatment after evaluating the patient's clinical condition, including symptom severity, co-occurring conditions, level of functioning, and available support system. The estimated degree of risk to self and to others is another significant determinant of treatment setting. Decisions about treatment setting should also include consideration of the patient's ability to adequately care for him- or herself, provide reliable feedback to the psychiatrist, and cooperate with treatment of the major depressive disorder.

Patients with suicidal or homicidal ideation, intention, or plans require close monitoring. For those at significant risk, measures such as hospitalization should be considered; hospitalization is usually indicated for patients who are considered to pose a serious threat of harm to themselves or others. Patients who refuse can be hospitalized involuntarily if their condition meets the criteria of the local jurisdiction for involuntary admission. Severely ill patients who lack or reject adequate social support outside of a hospital setting should be considered for admission to a hospital or intensive day program, if available. In addition, patients who also have complicating psychiatric or general medical conditions or who have not responded adequately to outpatient treatment may need to be hospitalized.

The optimal treatment setting and the patient's likelihood of benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment. Unfortunately, the spectrum of treatment settings available to patients is often limited by lack of availability of options in the geographic setting, lack of ability to pay for care, and/or limitations imposed by third party payers.

5. Evaluate functional impairment and quality of life

The assessment of a patient with major depressive disorder includes a determination of the severity and chronicity of symptoms. Even mild depression can impair function and threaten life and the quality of life. In the extreme, depressed people may be totally unable to function socially or occupationally or even to feed and clothe themselves and maintain minimal personal hygiene. Severely depressed patients may be immobilized to the point of being bedridden, with associated medical complications.

The psychiatrist should address impairments in functioning and help the patient to set specific goals appropriate to his or her functional impairments and symptom severity. This will likely involve helping the patient to establish intermediate, pragmatic steps in the course of recovery. For example, the psychiatrist may help patients who are having difficulty meeting commitments to develop a reasonable plan to fulfill their obligations (e.g., work, family obligations), potentially by making alternative arrangements. The psychiatrist may advise other patients not to make major life changes while in the midst of a major depressive episode. Impairments in the patient's overall quality of life should also be assessed, which can be done by asking pa-

tients what bothers them the most about their depression and determining how their current activities and enjoyment of life have been altered by their depressive symptoms. The overall goals of treatment of major depressive disorder should focus on alleviating functional impairments and improving quality of life in addition to achieving symptom resolution and episode remission.

6. Coordinate the patient's care with other clinicians

The psychiatrist should assure that a comprehensive assessment of general medical conditions is performed in order to identify factors that may precipitate or exacerbate depressive symptoms. He or she may initiate the medical evaluations or coordinate care with other appropriate clinicians. In some situations, review of medical records provided by the patient will suffice. In other situations, particularly when medical treatment is indicated, the psychiatrist should, with the patient's permission, arrange for collaborative care with other clinicians. Such collaboration may incorporate discussion of prescribed medication, including dose changes and possible drug interactions as well as necessary diagnostic procedures and medical monitoring, which may include laboratory measures and ECG (34).

In treating the patient's depressive illness, a multifaceted approach is typically required that may include provision of depression-focused psychotherapy, pharmacotherapy, ECT, or other therapeutic approaches. Under some circumstances, all aspects of treatment will be administered by one psychiatrist, and this model of care may improve integration of treatment components (35) or reduce overall treatment cost (36). In other situations, treatment may require the coordinated effort of several clinicians. This decision is frequently influenced by the clinicians' expertise in providing the indicated therapeutic modality, economic factors, availability of treatment, and by the patient's preferences. When this treatment model is used, one team member must assume the primary overall responsibility for the patient's care. This individual serves as the coordinator of the treatment plan, advocates for the appropriate level of care, oversees the family involvement, makes decisions regarding which potential treatment modalities are useful and which should be discontinued, helps assess the effects of medications, and monitors the patient's safety. Because of the diversity and depth of medical knowledge and expertise required for this oversight function, a psychiatrist is generally optimal for this role, although this staffing pattern may not be possible in some health care settings. If the treatment is split, the psychiatrist who is providing the psychiatric management and the medication treatment should meet with the patient frequently enough to monitor his or her care. Ongoing coordination of the overall treatment plan is essential and is enhanced by clear role definitions, plans for the management of crises or relapses, and regular communication among the clinicians who are involved in the treatment.

Psychiatrists may at times serve as consultants to ongoing treatment of depression by other prescribers. Health care professionals other than psychiatrists may prescribe antidepressant medication for their patients for a variety of reasons, including convenience, financial reasons, stigma, and access to care issues (37). Primary care doctors, obstetricians, and physicians of other disciplines may screen for depression and initiate treatment for patients. In fact, at least one-fourth of patients presenting to primary care settings may have major depressive disorder, and 70%–80% of antidepressants are prescribed by a primary care physician or medical subspecialist (38, 39). Regardless of whether the psychiatrist is acting as a consultant or transferring ongoing care to another clinician (e.g., with transition from an inpatient to outpatient setting), communication and coordination of treatment are essential. Optimal communication with other health care professionals can improve overall treatment by assuring that medical conditions and psychosocial issues are appropriately addressed. Good communication also decreases the risk that patients will receive inconsistent information about treatment options and risks and benefits. Furthermore, communication among clinicians improves vigilance against relapse, side effects, and risk to self or others.

7. Monitor the patient's psychiatric status

As treatment progresses, different features and symptoms of the patient's illness may emerge or subside. The psychiatrist should carefully and systematically monitor changes in the patient's psychiatric status, including major depressive disorder symptoms, as well as symptoms of other potential co-occurring conditions (Table 2). Monitoring the patient's status for the emergence of or changes in destructive impulses toward self or others is especially crucial; additional measures such as hospitalization or more intensive treatment should be considered for patients found to be at higher risk. In addition, the patient should be monitored for treatment-emergent side effects, some of which may be difficult to distinguish from symptoms of the underlying depressive disorder or co-occurring medical conditions. Significant changes in a patient's psychiatric status or the emergence of new symptoms may warrant a diagnostic re-evaluation of the patient. For example, patients who note worsening irritability, increased difficulty sleeping, racing thoughts, growing impulsivity, euphoria, or rapid shifts in mood should be monitored more closely and may warrant re-evaluation and consideration of a possible bipolar dis-

order diagnosis. Often family members or caregivers notice changes in the status of the patient first and are therefore able to provide valuable input to the psychiatrist.

8. Integrate measurements into psychiatric management

The integration of measurement tools into psychiatric management, which has been referred to as measurement-based care, may enhance the quality of care and improve clinical outcomes (40). Clinician-rated and/or self-rated scales can help determine the trajectory of disease course and effects of treatment. Many such scales are available in several versions that vary by number of items. Self-rated scales are convenient to use but require review, interpretation, and discussion with the patient. In research studies, commonly used tools include the Inventory of Depressive Symptoms (IDS), which is available in clinician-rated and self-rated versions (http://www.ids-qids.org/), the clinician-rated Hamilton Rating Scale for Depression (HAM-D) (http://healthnet.umassmed.edu/mhealth/HAMD.pdf) (41, 42), the clinician-rated Montgomery Asberg Depression Rating Scale (MADRS) (http://www.cnsforum.com/streamfile.aspx?filename=MADRS.pdfandpath=pdf) (43), and the self-rated 9-item Patient Health Questionnaire (PHQ-9) (http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/) (44, 45). The Beck Depression Inventory (BDI, BDI-II) is another commonly used, copyrighted, 21-question multiple-choice self-rated instrument (46).

Systematic measurement of side effects can also assist in the provision of treatment. Several self-report rating scales have been developed for assessing side effects of antidepressant treatment and are available in English and Spanish versions (http://www.edc.pitt.edu/stard/public/ assessment_forms.html). The Frequency, Intensity, and Burden of Side Effects Rating Scale (FIBSER), which has also been referred to as the Frequency and Intensity of Side Effects Rating/Global Rating of Side Effect Burden, uses three global Likert scale ratings to assess side effects experienced over the preceding week (47, 48). The Patient Rated Inventory of Side Effects (PRISE) is a 9-item scale that asks patients about the presence of side effects in eight organ system domains, as well as about other side effects (47, 48). A clinician-administered scale, the Toronto Side Effects Scale, that focuses on antidepressant medication side effects is also available (http://ww1.cpa-apc.org:8080/publications/archives/cjp/2002/march/orAntidepressantsAppendix.asp) (49). The Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (50) (available at http:/ /www.cnsforum.com/streamfile.aspx?filename=UKU. pdfandpath=pdf) is often used in research studies and may offer clinicians additional questions that could be asked about side effects, but it is likely to be too detailed for routine clinical use.

TABLE 2. Items to Monitor Throughout Treatment

Symptomatic status, including functional status, and quality of life
Degree of danger to self and others
Signs of "switch" to mania
Other mental disorders, including alcohol and other substance use disorders
General medical conditions
Response to treatment
Side effects of treatment
Adherence to treatment plan

Although the use of rating scales is not yet common practice in clinical settings, in part due to pragmatic concerns (51), the use of such scales can be valuable in monitoring symptoms and treatment progress. In addition, electronic monitoring is becoming more feasible, as electronic health records are more commonly utilized and patients and psychiatrists have increased access to technological tools that can help monitor and record symptoms. Baseline data and information about treatment-emergent changes can be collected systematically from the patient and electronically transmitted via telephone or the Internet. In addition to providing secure electronic capture of patient data, computerized decision support systems can be useful in implementing evidence-based treatment for major depressive disorder (52).

9. Enhance treatment adherence

For treatment to be successful, it is essential to support the patient's adherence to all details of the regimen by providing education about the illness and its treatment, maintaining a strong therapeutic alliance, mobilizing family and other supports (including eliciting questions and clarifying common misconceptions), evaluating factors affecting adherence, and addressing barriers to adherence as they arise. Major depressive disorder is often a chronic or recurrent condition that requires patients to participate actively in and adhere to treatment plans for long periods, despite the fact that side effects or requirements of treatments may be burdensome. Patients may have strong preferences for modality of treatment or medication choice, particularly if they or a family member have had past experience with the treatment or medication. When feasible, factoring in these preferences may improve adherence to treatment. During the acute phase, patients with major depressive disorder may be poorly motivated, unduly pessimistic about their chances of recovery with treatment, suffering from deficits in memory, or poorly caring for themselves. During the

maintenance phase, euthymic patients may undervalue the benefits of and focus on the burdens of treatment. The psychiatrist should recognize these possibilities, emphasize the importance of adherence for successful treatment and prophylaxis, and encourage the patient to articulate any concerns regarding adherence (e.g., side effects, costs of treatment, scheduling conflicts, lack of transportation or child care). Patient and family attitudes about depression and its treatment can also influence adherence. Family members can play an important role in promoting optimism about treatment, assisting patients with adherence and providing the psychiatrist with input on side effects or other treatment-related concerns that may influence adherence.

Some aspects of adherence will vary with the type of treatment being used. For example, patients in psychotherapy may experience increased anxiety as they confront fearful or difficult topics. This anxiety, in turn, may decrease adherence to psychotherapy, and patients may begin to arrive late to or miss therapy sessions. In patients who are beginning treatment with a medication, common side effects of medication options should be discussed. Patients should be involved in treatment decisions and encouraged to convey input on side effects that they consider reasonable or unbearable. Side effects such as weight gain, cognitive dulling, sexual side effects, sedation or fatigue, and agitation may represent different burdens to different individuals. Emphasizing the following specific topics improves adherence: 1) explaining when and how often to take the medicine; 2) suggesting reminder systems, such as pill boxes, alarms, etc.; 3) discussing the need to take medication for at least 2–4 weeks before beneficial effects may be noticed; 4) emphasizing the need to take medication even after feeling better; 5) reviewing the need to consult with the psychiatrist before discontinuing medication; 6) giving the patient an opportunity to express his or her understanding of the medication, hearing his or her concerns, and correcting any misconceptions, and 7) explaining what to do if problems or questions arise (53). Behavioral tailoring, which involves developing an individualized approach to incorporating medication into the daily routine and can also include simplifying the medication regimen, has demonstrated efficacy for individuals with schizophrenia and may also be applicable to individuals with other psychiatric illnesses (54). Adherence may also be improved by minimizing the cost and complexity of medication regimens. Most antidepressant medications are available in generic forms, which are generally less costly. For individuals who cannot afford needed medications, some pharmaceutical companies offer patient assistance programs. Information on such programs is available from pharmaceutical company Web sites, from the Web site of the Partnership for Prescription Assistance (http://www.helpingpatients.org), and from Rx Assist (http://www.rxassist.org).

10. Provide education to the patient and the family

Education concerning major depressive disorder and its treatments should be provided to all patients. Education is an essential element of obtaining informed consent to treatment. Whenever possible, education should also be provided to involved family members and significant others, although generally the patient's consent is required before such information can be shared. Specific topics to discuss may include that major depressive disorder is a medical illness and that effective treatments are both necessary and available. This information may be especially important for patients who attribute their illness to a moral defect, or for family members who are convinced that there is nothing wrong with the patient. Education regarding available treatment options will help patients make informed decisions, anticipate side effects, and adhere to treatments. Patients with depression can become easily discouraged in treatment, especially if there is less than a full initial response. The psychiatrist should encourage and educate patients to distinguish between the hopelessness that is a symptom of depression and the relatively hopeful actual prognosis. In addition, for patients treated with antidepressant medication or ECT, psychiatrists may choose to discuss a predictable progression of treatment effects: first, side effects may emerge, then neurovegetative symptoms remit, and finally mood improves. Often significant others notice symptomatic improvement before the patient does.

Given the chronic, episodic nature of major depressive disorder, exacerbations are common. Patients, as well as their families, if appropriate, should be instructed about the significant risk of relapse. They should be educated to identify early signs and symptoms of new episodes and the stressors that may precede them. Patients should also be instructed to seek adequate treatment as early in the course of the new episode as possible to decrease the likelihood of a full-blown exacerbation or complications.

Patient and family education also includes general promotion of healthy behaviors such as good sleep hygiene and decreased use of caffeine, tobacco, alcohol, and other potentially deleterious substances. For most individuals, exercise carries benefits for overall health. Data generally support at least a modest improvement in mood symptoms for patients with major depressive disorder who engage in aerobic exercise (55–61) or resistance training (62, 63). Regular exercise may also reduce the prevalence of depressive symptoms in the general population, with specific benefit found in older adults (64, 65) and individuals with co-occurring medical problems (57, 66).

B. ACUTE PHASE

1. Choice of initial treatment modality

The acute phase of treatment lasts a minimum of 6–12 weeks. During this phase, the aims of treatment are to induce remission of symptoms and achieve a full return to the patient's baseline level of functioning. In addition to general psychiatric management (described in Section II.A), treatment may consist of pharmacotherapy or other somatic therapies (e.g., ECT, light therapy), depression-focused psychotherapy, or the combination of somatic and psychosocial therapies. Selection of an initial treatment modality is influenced by several factors, including the symptom profile, the presence of co-occurring disorders or psychosocial stressors, the patient's prior treatment experience, and the patient's preference.

Psychiatrists should present patients with information concerning the evidence for a broad range of treatment options, including somatic therapies and psychosocial interventions. Antidepressant medications can be used as an initial treatment modality by patients with mild, moderate, or severe major depressive disorder. Clinical features that may suggest that medications are the preferred treatment modality include a history of prior positive response to antidepressant medications, the presence of moderate to severe symptoms, significant sleep or appetite disturbances, agitation, patient preference, and anticipation of the need for maintenance therapy. Patients with major depressive disorder with psychotic features require either the combined use of antidepressant and antipsychotic medications or ECT.

Psychotherapy may also be considered as monotherapy for patients with mild to moderate major depressive disorder. The availability of clinicians with appropriate training and expertise in specific psychotherapeutic approaches can be a factor in choosing a psychotherapy (67). Other factors that can influence this choice may be the psychosocial context, patient preference, prior positive response to psychotherapy, the presence of significant psychosocial stressors or interpersonal difficulties, co-occurring Axis II disorders, or the stage, chronicity, and severity of the major depressive episode. Specifically, many severely depressed patients will require both a depression-focused psychotherapy and a somatic treatment such as pharmacotherapy. Pregnancy, lactation, or the wish to become pregnant may tilt a decision toward psychotherapy as an initial treatment (see Section III.B.6). Given the lower occurrence of side effects and suggestion of enduring benefits associated with depression-focused psychotherapies (68), such treatments might be preferable alternatives to pharmacotherapy for some patients with mild to moderate depression.

Combining a depression-focused psychotherapy and pharmacotherapy may be a useful initial treatment choice for patients with moderate to severe major depressive disorder. Other indications for combined treatment include chronic forms of depression, psychosocial issues, intrapsychic conflict, interpersonal problems, or a co-occurring Axis II disorder. In addition, patients who have had a history of only partial response to adequate trials of single treatment modalities may benefit from combined treatment. Poor adherence with pharmacotherapy may also warrant combined treatment with medications and psychotherapy focused on treatment adherence.

Electroconvulsive therapy should be considered as a potential treatment option for all patients with major depressive disorder who have psychotic features or catatonia and for those with an urgent need for response, such as patients who are suicidal or who are nutritionally compromised as a result of refusing food. Electroconvulsive therapy may also be the treatment modality of choice for patients with major depressive disorder who have a high degree of symptom severity. Other considerations include the presence of co-occurring general medical conditions that preclude the use of antidepressant medications, a prior history of positive response to ECT, and patient preference. Evidence for TMS is currently insufficient to support its use in the initial treatment of major depressive disorder.

If a patient with mild depression wishes to try exercise alone for several weeks as a first intervention, there is little to argue against it (Section II.A.10), provided the patient is sufficiently monitored for an abrupt worsening of mood or adverse physical effects (e.g., ischemia or musculoskeletal symptoms). The dose of exercise and adherence to an exercise regimen may be particularly important to monitor in the assessment of whether an exercise intervention is useful for major depressive disorder (69, 70). If mood fails to improve after a few weeks with exercise alone, the psychiatrist should recommend medication or psychotherapy. For patients with depression of any severity and no medical contraindication to exercise, physical activity is a reasonable addition to a treatment plan for major depressive disorder. The optimal regimen is one the patient prefers and will adhere to.

Figure 1 summarizes treatment modalities that may be appropriate during the acute phase of treatment depending on the severity of the patient's symptoms and other associated features of the depressive episode. It is important to note that other factors may be relevant to treatment decisions for individual patients and that determinations of episode severity are imprecise, although rating scales may be helpful in assessing the magnitude of depressive symptoms and their effects on functional status and quality of life (see Sections II.A.7 and II.A.8).

	Modality			
Severity of Illness	Pharmacotherapy	Depression-Focused Psychotherapy	Pharmacotherapy in Combination With Depression-Focused Psychotherapy	Electroconvulsive Therapy
Mild to Moderate	Yes	Yes	May be useful for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder	Yes, for certain patients
Severe Without Psychotic Features	Yes	No	Yes	Yes
Severe With Psychotic Features	Yes, provide both antidepressant and antipsychotic medication	No	Yes, provide both antidepressant and antipsychotic medication	Yes

FIGURE 1. Recommended Modalities for Acute Phase Treatment of Major Depressive Disorder

2. Pharmacotherapy

Antidepressant medications have been grouped as follows: 1) TCAs, which for the purposes of this guideline also include the tetracyclic antidepressant medication maprotiline; 2) SSRIs, which include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram; 3) SNRIs, which include venlafaxine, desvenlafaxine, and duloxetine; 4) other antidepressant medications, including bupropion, nefazodone, trazodone, and mirtazapine; and 5) MAOIs, which include phenelzine, tranylcypromine, isocarboxazid, and the transdermal formulation of selegiline. Although some studies have suggested superiority of one mechanism of action over another, there are no replicable or robust findings to establish a clinically meaningful difference. For most patients, the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Response rates in clinical trials typically range from 50% to 75% of patients, with some evidence suggesting greater efficacy relative to placebo in individuals with severe depressive symptoms as compared with those with mild to moderate symptoms (71–73). Although remission rates are less robust and selective publication of positive studies could affect the apparent effectiveness of treatment (74, 75), these factors do not appear specific to particular medications or medication classes.

Nevertheless, antidepressant medications do differ in their potential to cause particular side effects such as adverse sexual effects, sedation, or weight gain. Therefore, the initial selection of an antidepressant medication will largely be based on the tolerability, safety, and cost of the medication, as well as patient preference and history of prior medication treatment (Table 3). Other factors include the medication half-life and potential for drug interactions related to properties such as plasma protein binding or metabolism through the cytochrome P450 system (Tables 4 and 5). On the basis of these considerations, the following medications are optimal for most patients: SSRIs, SNRIs, mirtazapine, and bupropion. Table 6 provides the starting and usual doses of medications that have been shown to be effective for treating major depressive disorder.

TABLE 3. Factors to Consider in Choosing an Antidepressant Medication

Patient preference
Nature of prior response to medication
Relative efficacy and effectiveness
Safety, tolerability, and anticipated side effects
Co-occurring psychiatric or general medical conditions
Potential drug interactions
Half-life
Cost

TABLE 4. Cytochrome P450 Enzyme Metabolism of Antidepressive Agents[a]

	1A2	2B6	2C9	2C19	2D6	3A4
Amitriptyline	+	+	++	++	++	+
Bupropion	+	++	+		+	
Hydroxybupropion[b]					++	
Citalopram				++	+	++
Desipramine	+				++	
Desvenlafaxine						+
Duloxetine	++				++	
Escitalopram				++	+	+
Fluoxetine	+	+	++	+	++	+
Norfluoxetine[b]					+++	
Imipramine	++	+		++	++	++
Maprotiline	+				++	
Mirtazapine	++		+		++	+
8-Hydroxymirtazapine[b]					++	++
Mirtazapine-*N*-oxide[b]						++
Nortriptyline	+			+	++	+
Paroxetine					++	
Protriptyline					++	
Selegiline	+	++		+	+	
Sertraline		++	+	++	+	+
Venlafaxine			+	+	++	+
O-Norvenlafaxine[b]					++	

Sources: (82, 83). The extent to which each medication is a substrate for a specific enzyme is indicated as follows: +++ = exclusive substrate, ++ = major substrate, + = minor substrate.

[a]Information about drug metabolism and drug-drug interactions is constantly evolving. The information in this table can serve as a guide; however, the reader is encouraged to access regularly updated online sources of drug-drug interactions.

[b]Active metabolite of parent compound.

In choosing an antidepressant medication, many psychiatrists also consider the family history of response to particular medications; however, the impact of this factor on the likelihood of the patient's response to these medications is unclear. Nevertheless, the medication experiences of others close to the patient do influence the patient's belief about particular medications and pharmacotherapy in general.

The presence of co-occurring psychiatric or general medical conditions can be a significant factor influencing the choice of an antidepressant medication. For example, TCAs are generally not optimal in patients with cardiovascular conditions, cardiac conduction defects, closed angle glaucoma, urinary retention, significant prostatic hypertrophy, or eating disorders with significant malnutrition or purging. In older adults and others with malnutrition, autonomic disorders (e.g., diabetic neuropathy, Parkinson's disease), or low blood pressure, TCAs may exacerbate hypotension and orthostasis, resulting in syncope or falls. Selective serotonin reuptake inhibitors and SNRIs may be inappropriate for patients who are experiencing sexual dysfunction. Patients who are receiving tamoxifen for breast cancer or other indications should generally be treated with an antidepressant (e.g., citalopram, escitalopram, venlafaxine, desvenlafaxine) that has minimal effect on metabolism through the cytochrome P450 2D6 isoenzyme, because reduced metabolism of tamoxifen through CYP 2D6 is likely to be associated with lower levels of tamoxifen's active metabolite (76–79) with the possibility of poorer patient outcomes (80, 81).

TABLE 5. Cytochrome P450 Enzyme Inhibition by Antidepressive Agents[a]

	1A2	2A6	2B6	2C8	2C9	2C19	2D6	2E1	3A4
Amitriptyline	+				+			+	
Bupropion							+++		
Citalopram	+		+			+	+		
Desipramine[b]		++	++				++	+	++
Desvenlafaxine									+
Duloxetine							++		
Escitalopram							++		
Fluoxetine	++		++	++	+	++	+++		+
Norfluoxetine[c]	+		++		+		++		+
Imipramine	+					+	+		+
Mirtazapine	+								+
Nortriptyline[d]				++			+	+	++
Paroxetine	+		+++		+	+	+++		+
Selegiline	+	+			+	+	+	+	+
Sertraline	+		++	+	+	++	++		++
Desmethylsertraline[c]			+		+		+		+
Venlafaxine			+				+		+

Sources: (82, 83). The extent to which each medication is a substrate for a specific enzyme is indicated as follows: +++ = strong inhibitor, ++ = moderate inhibitor, + = weak inhibitor.

[a]Information about drug metabolism and drug-drug interactions is constantly evolving. The information in this table can serve as a guide; however, the reader is encouraged to access regularly updated online sources of drug-drug interactions.

[b]Also a metabolite of imipramine. [c]Active metabolite of parent compound. [d]Also a metabolite of amitriptyline.

Because of the need for dietary restrictions and the potential for serious side effects and drug interactions, use of MAOIs is generally limited to patients who do not respond to other treatments. MAOIs may be particularly effective for patients with major depressive disorder with atypical features, although many psychiatrists prefer to prescribe SSRIs for such patients because of SSRIs' greater safety and tolerability and more favorable adverse effect profile.

a. Efficacy of antidepressant medications

1. Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors currently available include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. A large body of literature supports the superiority of SSRIs compared with placebo in the treatment of major depressive disorder. In more than 10 systematic reviews and meta-analyses, the effectiveness of SSRIs has been compared with that of other antidepressant medications, mainly TCAs. The SSRIs have demonstrated comparable efficacy to the TCAs (84–88), even when anxiety symptoms are considered (85, 87–90).

Although a few analyses suggest small advantages of SNRIs over SSRIs in rates of remission (91), a preponderance of the data finds no significant evidence of the superiority of any other class or agents over SSRIs (84, 89, 90, 92–95). One meta-analysis suggests a slight superiority of escitalopram compared with other SSRIs and venlafaxine (93), and another found significantly greater efficacy for escitalopram, sertraline, venlafaxine, and mirtazapine as compared with duloxetine, fluoxetine, fluvoxamine, and paroxetine (96), but other studies show no differences in efficacy among individual SSRIs (84, 93–95, 97, 98).

2. Serotonin norepinephrine reuptake inhibitors

The serotonin norepinephrine reuptake inhibitors currently available are venlafaxine, desvenlafaxine (the principal metabolite of venlafaxine), and duloxetine. An immediate-release form of venlafaxine is available, but most clinicians prefer the extended-release formulation because it is approved for once-daily dosing and may be less often associated with reported withdrawal symptoms.

TABLE 6. Dosing of Medications Shown To Be Effective in Treating Major Depressive Disorder[a]

Generic Name	Starting Dose (mg/day)[b]	Usual Dose (mg/day)[c]
Selective serotonin reuptake inhibitors[d]		
Citalopram	20	20–60[e]
Escitalopram	10	10–20
Fluoxetine	20	20–60[e]
Paroxetine	20	20–60[e]
Paroxetine, extended release	12.5	25–75
Sertraline	50	50–200[e]
Dopamine norepinephrine reuptake inhibitor[d]		
Bupropion, immediate release	150	300–450
Bupropion, sustained release	150	300–400
Bupropion, extended release	150	300–450
Serotonin norepinephrine reuptake inhibitors[d]		
Venlafaxine, immediate release	37.5	75–375
Venlafaxine, extended release	37.5	75–375
Desvenlafaxine	50	50[f]
Duloxetine	60	60–120
Serotonin modulators		
Nefazodone	50	150–300
Trazodone[g]	150	150–600
Norepinephrine-serotonin modulator		
Mirtazapine[d]	15	15–45
Tricyclics and tetracyclics		
Amitriptyline	25–50	100–300
Doxepin	25–50	100–300
Imipramine	25–50	100–300
Desipramine	25–50	100–300
Nortriptyline	25	50–200
Trimipramine	25–50	75–300
Protriptyline	10–20	20–60
Maprotiline	75	100–225
Monoamine oxidase inhibitors (MAOIs)		
Irreversible, nonselective inhibitors		
Phenelzine	15	45–90
Tranylcypromine	10	30–60
Isocarboxazid	10–20	30–60
Irreversible, MAO B selective inhibitor		
Selegiline transdermal[h]	6	6–12
Reversible MAO A selective inhibitor		
Moclobemide	150	300–600

[a]For convenience, medications other than TCAs have been classified by their presumptive mechanism of action. However, the exact mechanism of action of several medications has yet to be determined or varies by dose. [b]Lower starting doses are recommended for elderly patients and for patients with panic disorder, significant anxiety or hepatic disease, and co-occurring general medical conditions. [c]For some of these medications (e.g., TCAs) the upper dosing limit reflects risk of toxicity or need for plasma level assessment, whereas for other medications (e.g., SSRIs), higher doses can be used safely but without evidence for overall superior efficacy. [d]These medications are likely to be optimal medications in terms of safety, the patient's acceptance of side effects, and the quantity and quality of clinical trial data. [e]Dose varies with diagnosis; see text for specific guidelines. [f]Has been used at doses up to 400 mg/day, although doses above 50 mg/day may not provide additional benefit. [g]This medication is not typically used for this indication. [h]Selegiline selectively inhibits MAO B at low doses but inhibits both MAO A and MAO B at the higher doses that are typically required for antidepressant activity.

Each of these medications is efficacious (i.e., superior to placebo in controlled studies and meta-analyses) (95, 99), and venlafaxine (75–150 mg/day) and duloxetine (60 mg/day) showed comparable efficacy in a pair of trials (100). For venlafaxine and perhaps desvenlafaxine, clinically significant norepinephrine reuptake inhibition may not be achieved for the average patient at lower therapeutic doses, although desvenlafaxine has a much greater bioavailability, resulting in a lower effective dose. In individual studies, venlafaxine and duloxetine are generally as effective as SSRIs (see the meta-analyses of Nemeroff et al. [101] and Thase et al. [102] for tabulated summaries of individual study results from the more than 40 relevant randomized controlled trials). Results of comparative studies of desvenlafaxine are not known at this time. Relative to SSRIs, some analyses of pooled data sets have suggested a small advantage for SNRIs (91), which might afford clinically modest benefits for patients with more severe depression (102) or for patients who have not responded to prior trials of SSRIs (103). However, other meta-analyses have shown equivalent efficacy for SSRIs and SNRIs (95), whereas some have shown superiority of individual medications but no clearcut medication class effects (96). Relative to TCAs, venlafaxine's efficacy is comparable (91, 104, 105), whereas the more recently introduced duloxetine and desvenlafaxine have not been systematically compared with TCAs.

3. Other antidepressant medications

A number of other antidepressant medications differ structurally or in their pharmacological action from medications in the categories just described and are included here.

Although bupropion is classified as a norepinephrine and dopamine reuptake inhibitor, the latter effect is relatively weak, and its mechanism of action remains unclear (106). There are three formulations of bupropion: immediate release, sustained release, and extended release. Bupropion is distinct from most antidepressants in not having an indication for the treatment of any primary anxiety disorder, and it may be less well tolerated than other antidepressants among patients with significant anxiety. In addition, a meta-analysis showed that SSRIs were modestly superior to bupropion for a subset of patients with major depressive disorder and anxiety (107). For individuals with low to moderate levels of anxiety, the same meta-analysis showed that the efficacy of bupropion in treating major depressive disorder was roughly comparable to that of the SSRIs (107). Results of another meta-analysis suggested that bupropion may be more likely to improve symptoms of fatigue and sleepiness than at least some of the SSRIs (108). Bupropion may be a good choice for patients who have a goal of quitting smoking as it has U.S. Food and Drug Administration (FDA) approval for this indication, reduces desire for nicotine, and doubles rates of smoking cessation (109, 110). Patients typically experience minimal weight gain or even weight loss on bupropion (111), and for this reason it may be an appropriate antidepressant for patients who are overweight or obese.

Mirtazapine is thought to work through noradrenergic and serotonergic mechanisms, although this tetracyclic compound is not a reuptake inhibitor (112). Mirtazapine has comparable efficacy to SSRIs (113).

Trazodone is the oldest medication from this group that is still in wide use. Although trazodone is an effective antidepressant, relative to placebo (105, 114, 115), in contemporary practice it is much more likely to be used in lower doses as a sedative-hypnotic than as an antidepressant. Despite widespread use of trazodone as a hypnotic, few data support its use for this indication.

Nefazodone has an analogous structure to trazodone but somewhat different pharmacological properties. In comparative trials versus SSRIs, nefazodone showed comparable efficacy and overall tolerability (116).

4. Tricyclic antidepressants

Tricyclic antidepressants (amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine) are effective treatments for major depressive disorder and have comparable efficacy to other classes of antidepressants, including SSRIs, SNRIs, and MAOIs (85, 105). The efficacy of subclasses of tricyclics (e.g., secondary amines or tertiary amines) appears to be comparable. TCAs may be particularly effective in certain populations, such as in hospitalized patients (117, 118). Conventional wisdom is that this advantage is explained by the superiority of TCAs (versus SSRIs) among the subset of patients with melancholia or more severe depression, because such a specific advantage has not been consistently documented in studies of less severely ill outpatients (85, 105, 118).

5. Monoamine oxidase inhibitors

MAOIs currently used as antidepressants include phenelzine, tranylcypromine, isocarboxazid, moclobemide, and the transdermally delivered formulation of selegiline.

MAOIs have comparable efficacy to other antidepressants for outpatients with major depressive disorder and may be appropriate for patients with major depressive disorder who have not responded to safer and more easily used treatments (119, 120). In fact, the role of MAOIs in major depressive disorder is now almost exclusively reserved for patients who have not responded to at least several other pharmacotherapies. Studies have demonstrated the effectiveness of MAOIs in patients who have not responded to other antidepressant medications, particularly

TCAs (119). However, the effectiveness of MAOIs relative to other strategies for treatment-resistant patients in contemporary practice remains unclear, particularly for patients who have not responded to multiple sequential trials with SSRIs and SNRIs (121).

MAOIs have been shown to be particularly effective in treating depressed patients with atypical features, so psychiatrists should consider using these medications for patients with symptoms such as reactive moods, reverse neurovegetative symptoms, and sensitivity to rejection (119, 120, 122). There do not appear to be any significant differences in efficacy among the older MAOIs (119), although there are important individual differences in responsiveness, and these medications are not interchangeable. There are no comparative studies of the newer transdermal (skin patch) formulation of selegiline; its efficacy has only been established relative to placebo (123–125), and clinical experience is limited.

b. Side effects of antidepressant medications

The severity of side effects from antidepressant medications in clinical trials has been assessed both through the frequency of reported side effects and through the frequency of treatment dropout. The likelihood of different side effects varies among classes of antidepressant medications, among subclasses, and among individual agents. In addition, most newer antidepressants are better tolerated than TCAs (84–88, 97, 117, 126) and safer in overdose (127, 128).

When side effects occur during treatment with an antidepressant, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect. As an example, bupropion can be used if patients encounter sexual side effects with an SSRI medication. When lowering the dose or discontinuing the medication is not effective, additional strategies may be considered. These additional strategies are described in Table 7, which also lists prominent and clinically relevant side effects associated with particular medication classes.

Serotonin syndrome, as the name implies, is presumed to result from high levels of serotonin in the brain. Although it can occur with administration of one or more serotonergic medications, it is most severe when an MAOI is coadministered with another serotonergic medication. Consequently, great care must be taken when changing patients from another antidepressant medication to an MAOI and from an MAOI to other antidepressant medications because of the persistent effects of discontinued medications. A washout period is essential before and after using an MAOI. If the psychiatrist chooses to discontinue a monoamine-uptake-blocking antidepressant medication (e.g., SSRI, SNRI, TCA) and substitute an MAOI, toxic interactions can best be avoided by allowing at least a 2-week washout period between medication trials (Table 8). The long half-life of the SSRI fluoxetine and its metabolites necessitates a 5- to 6-week washout period or longer before the use of an MAOI. Additional information about serotonin syndrome with specific medication classes can be found in Sections II.B.2.b.1.g. and II.B.2.b.5.b.

Because knowledge of potential drug-drug interactions is frequently changing, it is useful to consult a frequently updated drug information database before selecting an antidepressant in a patient taking other medications.

1. Selective serotonin reuptake inhibitors

SSRIs have comparable tolerability overall, but the specific medications differ somewhat in their side effect profiles, which may guide selection of an agent for an individual patient. Pharmacokinetic issues, including half-life and effect on the CYP-450 enzyme system, are additional considerations in the choice of an SSRI.

a. Gastrointestinal

SSRIs commonly cause nausea, vomiting, and diarrhea (98). These adverse events are generally dose dependent and tend to dissipate over the first few weeks of treatment. In some patients, however, diarrhea persists.

b. Activation/insomnia

SSRIs sometimes precipitate or exacerbate restlessness, agitation, and sleep disturbances—side effects that often attenuate with time. Anxiety may be minimized by introducing the agent at a low dose. Akathisia has also been reported in patients taking SSRIs (129) and may contribute to reported restlessness or activation. If akathisia does occur, a beta-blocker or benzodiazepine can be tried to reduce symptoms. Insomnia can be treated by using sleep hygiene techniques or CBT as a first approach or by adding a sedative-hypnotic medication or trazodone. Some have found melatonin to be helpful in treating SSRI-induced insomnia.

c. Sexual side effects

Although loss of erectile or ejaculatory function in men and loss of libido and anorgasmia in both sexes may be complications of virtually any antidepressant medication, these side effects appear to be more common with SSRIs. The psychiatrist should ascertain whether the reported sexual dysfunction is a result of the antidepressant medication, the underlying major depressive disorder, a co-occurring medical disorder, a disturbance in a relationship, or a need for education about sexual functioning. If sexual dysfunction is determined to be a side effect of the antidepressant medication, a number of strategies are available, including

TABLE 7. Potential Treatments for Side Effects of Antidepressant Medications

Side Effect	Antidepressant Associated With Effect	Treatment[a]
Cardiovascular		
Arrhythmias	TCAs	Avoid in patients with cardiac instability or ischemia. Attend to interactions with anti-arrhythmics.
Hypertension	SNRIs, bupropion	Monitor blood pressure. Keep dose as low as possible. Add antihypertensive.
Hypertensive crisis	MAOIs	Seek emergency treatment. If hypertension is severe, intravenous antihypertensive agents (e.g., labetalol, sodium nitroprusside) may be required.
Increase in cholesterol	Mirtazapine	Add a statin.
Orthostatic hypotension	TCAs, trazodone, nefazodone, MAOIs	Add fludrocortisone. Add salt to diet.
Anticholinergic		
Constipation	TCAs	Encourage adequate hydration. Add bulk laxative.
Delirium	TCAs	Evaluate for other possible contributors to delirium.
Dry mouth	TCAs, SNRIs, bupropion	Suggest use of sugarless gum or candy.
Urinary hesitancy	TCAs	Add bethanechol.
Visual changes	TCAs	Add pilocarpine eye drops.
Neurologic		
Headaches	SSRIs, SNRIs, bupropion	Assess for other etiologies (e.g., caffeinism, bruxism, migraine, tension headache).
Myoclonus	TCAs, MAOIs	Add clonazepam.
Seizures	Bupropion, TCAs, amoxapine	Assess for other etiologies, and add anticonvulsant medication, if clinically indicated.
Sexual		
Arousal, erectile dysfunction	TCAs, SSRIs, SNRIs	Add sildenafil, tadalafil, buspirone, or bupropion.
Orgasm dysfunction	TCAs, SSRIs, venlafaxine, desvenlafaxine, MAOIs	Add sildenafil, tadalafil, buspirone, or bupropion.
Priapism	Trazodone	Obtain emergency urological evaluation.
Other		
Activation	SSRIs, SNRIs, bupropion	Administer in the morning.
Akathisia	SSRIs, SNRIs	Add a beta-blocker or benzodiazepine.
Bruxism	SSRIs	Obtain dental consultation, if clinically indicated
Diaphoresis	TCAs, some SSRIs, SNRIs	Add an α_1-adrenergic antagonist (e.g., terazosin), central α_2-adrenergic agonist (e.g., clonidine), or anticholinergic agent (e.g., benztropine).
Fall risk	TCAs, SSRIs	Monitor blood pressure for evidence of hypotension or orthostasis; assess for sedation, blurred vision, or confusion; modify environment to reduce risk.
Gastrointestinal (GI) bleeding	SSRIs	Identify whether concomitant medications may affect clotting.

(continued)

TABLE 7. Potential Treatments for Side Effects of Antidepressant Medications *(continued)*

Side Effect	Antidepressant Associated With Effect	Treatment[a]
Other *(continued)*		
Hepatotoxicity	Nefazodone	Provide education about and monitor for clinical evidence of hepatic dysfunction. Obtain hepatic function tests, if clinically indicated.
Insomnia	SSRIs, SNRIs, bupropion	Use morning dosing. Add a sedative-hypnotic at bedtime. Add melatonin. Provide CBT or education in sleep hygiene.
Nausea, vomiting	SSRIs, SNRIs, bupropion	Administer after food or in divided doses.
Osteopenia	SSRIs	If clinically indicated, obtain bone density monitoring and add specific treatment to reduce bone loss (e.g., calcium and vitamin D supplements, bisphosphonates, selective estrogen receptor agents).
Sedation	TCAs, trazodone, nefazodone, mirtazapine	Use bedtime dosing. Add modafinil or methylphenidate.
Severe serotonin syndrome	MAOIs	Obtain emergency evaluation. Consider admission to a critical care unit.
Weight gain	SSRIs, mirtazapine, TCAs, MAOIs	Encourage exercise. Obtain input from dietician. If changing antidepressants, consider a secondary amine (if a TCA is required) or other antidepressant with fewer weight issues (e.g., bupropion).

[a]Initial approaches to treatment-emergent side effects include decreasing or discontinuing the medication and changing to another antidepressant with a different side effect profile. Treatments included here are additional measures.

continuing treatment to assess whether the dysfunction will disappear with time, lowering the dose, discontinuing the antidepressant, or substituting another antidepressant such as bupropion (130). Specific pharmacological treatments that can be added for arousal difficulties, erectile dysfunction, or orgasm dysfunction include buspirone (131), bupropion (132), sildenafil (133), and tadalafil (134). Other phosphodiesterase inhibitors may be also useful in treating sexual side effects, and a variety of other medications have been used with anecdotal success (135, 136).

d. Neurological effects

Selective serotonin reuptake inhibitors can initially exacerbate both migraine headaches and tension headaches. These effects tend to be transient and improve within the first few weeks of treatment. With continued treatment, SSRIs may actually help prevent and treat migraine headaches (137, 138). Selective serotonin reuptake inhibitors have also been associated with extrapyramidal side effects, including akathisia, dystonia, parkinsonism, and tardive dyskinesia (139, 140). The incidence of such side effects is very low with SSRIs but may be higher in older patients, especially those with Parkinson's disease.

e. Falls

Selective serotonin reuptake inhibitors, like other antidepressive agents, have been associated with an increased risk of falls. In studies of nursing home residents, SSRI use has been associated with an approximately twofold increase in the risk of a fall (141, 142). An even greater risk of falls in patients who were taking SSRIs was noted in a community-based cohort study (143). Meta-analyses have also documented an increased risk of falls in patients treated with antidepressive agents, in general (144, 145). The implications of this increase in fall risk are complicated by the decrease in bone density that has been noted in depressed patients (146) and in patients treated with SSRIs (147, 148). An increase in the risk of hip fractures has also been noted (149). Rarely, SSRI use has been associated with bradycardia, which could also contribute to syncope and falls (150). In all patients, including those treated with SSRIs, fall risk may be increased in individuals receiving benzodiazepines or other hypnotic agents (144, 145, 151) and in those receiving multiple medications (144, 145). Systematically reviewing patients' medication regimens may help to eliminate medications that

TABLE 8. Required Washout Times Between Antidepressant Trials

To	From	Minimum Washout Period (weeks)
MAOI	Drug with long-half-life metabolites (e.g., fluoxetine)	5–6
	Drug without long-half-life metabolites (e.g., TCAs, paroxetine, fluvoxamine, venlafaxine)	2
	MAOI	2
Non-MAOI	MAOI	2

may no longer be needed, although such interventions have not been found to alter fall risk, per se (152). Inquiring about a history of falls in the past year and assessing for abnormalities in gait and balance can also help in identifying patients at particular risk for falling (153).

f. Effects on weight

Weight gain, at times substantial, occurs in some patients taking SSRIs (154). Patients who take paroxetine have a higher incidence of weight gain than those who take other SSRIs (98, 155). Fluoxetine causes an initial reduction in weight, which tends to normalize with continued treatment (156).

g. Serotonin syndrome

Use of SSRIs has been associated with the rare development of a syndrome caused by an excess of central nervous system serotonergic activity. Features of serotonin syndrome include abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status changes, tremor and myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and possibly death (157). Although serotonin syndrome can occur rarely with the use of SSRIs alone, it is usually associated with the simultaneous use of multiple serotonergic agents and is most severe when SSRIs are given together with MAOIs. Consequently, when an SSRI is being changed to an MAOI or vice versa, particular attention must be give to the duration of time between treatments (Section II.B.2.b) to avoid precipitating a potentially lethal serotonin syndrome. Serotonin syndrome has also been reported when SSRIs are used in combination with tramadol, high-dose triptans, or the antibiotic linezolid, which also has some ability to inhibit MAO (158, 159).

h. Drug interactions

The potential for drug-drug interactions differs significantly across the SSRIs. Selective serotonin reuptake inhibitors have variable effects on hepatic microsomal enzymes and therefore cause both increases and decreases in the blood levels of other medications. For example, when SSRIs that strongly inhibit the CYP 2D6 isoenzyme (e.g., paroxetine, fluoxetine) are administered concomitantly with tamoxifen, the metabolism of tamoxifen to its active metabolite is reduced (76–79), resulting in a potential decrease in its efficacy in preventing breast cancer relapse (80, 81). Interaction with other drugs was higher for fluoxetine, fluvoxamine, and paroxetine than for sertraline, citalopram, and escitalopram (98, 160, 161).

As described above, there can be a potentially lethal interaction between SSRIs and MAOIs: the serotonin syndrome. At least five half-lives should elapse between the time an SSRI is stopped and an MAOI is started; for fluoxetine discontinuation, this means waiting approximately 5–6 weeks before starting an MAOI; for discontinuation of other SSRIs, approximately 2 weeks should pass before starting an MAOI (162). A 2-week waiting period has been suggested after discontinuing an MAOI before starting an SSRI or another MAOI (Table 8).

i. Discontinuation syndrome

Selective serotonin reuptake inhibitors generally should not be abruptly discontinued after extended therapy and, whenever possible, should be tapered over several weeks to minimize discontinuation-emergent symptoms. Clinical experience and a few controlled studies suggest that among the SSRIs, discontinuation-emergent symptoms are more likely with paroxetine than sertraline, citalopram, or escitalopram and least likely to occur with fluoxetine (due to the long elimination half-life of its primary metabolite, norfluoxetine) (163, 164). Discontinuation-emergent symptoms include both flu-like experiences such as nausea, headache, light-headedness, chills, and body aches, and neurological symptoms such as paresthesias, insomnia, and "electric shock-like" phenomena. These symptoms typically resolve without specific treatment over 1–2 weeks. However, some patients do experience more protracted discontinuation syndromes, particularly those treated with paroxetine, and may require a slower downward titration regimen. Another strategy is to change to a brief course of fluoxetine, e.g., 10 mg for 1–2 weeks, and then taper and discontinue the fluoxetine (165).

2. *Serotonin norepinephrine reuptake inhibitors*

The most common side effects of the SNRIs (venlafaxine, desvenlafaxine, and duloxetine) are similar to those seen with SSRIs, including nausea and vomiting, sexual dysfunction, and activation; like the side effects seen with SSRIs, those with SNRIs can attenuate with continued use. The SNRIs also are more likely to be associated with side effects that reflect noradrenergic activity, including increased pulse rate, dilated pupils, dry mouth, excessive sweating, and constipation. Although all three SNRIs carry the warning of increased blood pressure, this risk is greater during therapy with venlafaxine at doses above 150 mg/day (166) than with duloxetine at doses of 60–120 mg/day (167) or desvenlafaxine at doses of 50–100 mg/day (168). Because this blood pressure increase is dose-related, SNRI-induced hypertension may respond to dose reduction. In the absence of a reduction in hypertension, a different antidepressant medication may be considered. Alternatively, in a patient with well-controlled depressive symptoms, it may be preferable to add an antihypertensive agent rather than risk a depressive relapse or recurrence with medication tapering. As with the SSRIs, abrupt discontinuation of SNRIs should be avoided whenever possible. Discontinuation symptoms, which are sometimes protracted, are more likely to occur with venlafaxine (and, by implication, desvenlafaxine) than duloxetine (100) and may necessitate a slower downward titration regimen or change to fluoxetine. As described above (Section II.B.2.b), there can be a potentially lethal interaction between SNRIs and MAOIs: the serotonin syndrome.

3. *Other antidepressant medications*

a. Bupropion

Bupropion differs from other modern antidepressants by its lack of direct effects on serotonergic neurotransmission and, as a consequence, a virtual lack of sexual side effects (169). Neurologic side effects with bupropion include headaches, tremors, and seizures (106). The risk of seizures is minimized by avoiding high doses (e.g., using no more than 450 mg/day), avoiding rapid titration, using divided dosing schedules for the immediate-release and sustained-release formulations, and avoiding use of bupropion in patients with risk factors for seizures. Bupropion should also not be used in patients who have had anorexia nervosa or bulimia nervosa because of elevated risk of seizures (170). The risk of seizures may also be increased by the concomitant use of inhibitors of CYP 2B6 (e.g., desipramine, sertraline, paroxetine, fluoxetine) due to the resulting increase in bupropion blood levels. Bupropion has been associated with a low risk of psychotic symptoms, including delusions and hallucinations. It should therefore be used cautiously in patients with psychotic disorders. Other side effects with bupropion include agitation, jitteriness, mild cognitive dysfunction, insomnia, and gastrointestinal upset.

b. Mirtazapine

The most common side effects of mirtazapine include dry mouth, sedation, and weight gain. For this reason, mirtazapine is often given at night and may be chosen for depressed patients with initial insomnia and weight loss. Although these side effects tend to occur early in the treatment course and may attenuate with continued use, the weight gain associated with mirtazapine is greater than that with other non-TCA, non-MAOI antidepressants (95) and may make it a less attractive choice for some patients. Mirtazapine increases serum cholesterol levels in some patients (171). Although several patients treated with mirtazapine were observed to have agranulocytosis in early studies, subsequent clinical experience has not confirmed an elevated risk (172).

c. Trazodone

The most common side effect with trazodone is sedation. Because the sedation associated with trazodone is greater than that with other non-TCA, non-MAOI antidepressants (95), this can be an advantage in patients with initial insomnia (173). Trazodone can also cause cardiovascular side effects, including orthostasis, particularly among elderly patients or those with preexisting heart disease. Use of trazodone has also been associated with life-threatening ventricular arrhythmias in several case reports (173). Trazodone also can cause sexual side effects, including erectile dysfunction in men; in rare instances, priapism occurs, which might require surgical correction (174, 175).

d. Nefazodone

Side effects with nefazodone include dry mouth, nausea, constipation, orthostasis, and visual alterations (176). Sedation is also common and may necessitate a gradual titration of nefazodone. However, in patients with insomnia, the sedating properties of nefazodone can be helpful in improving sleep (177). There appears to be a low incidence of treatment-emergent sexual dysfunction (178, 179) with nefazodone and, unlike trazodone, it has not been associated with priapism. Nefazodone has also been associated with rare but potentially fatal liver failure (180, 181), which has limited its use in recent years. Drug-drug interactions can also be problematic as nefazodone inhibits hepatic microsomal enzymes and can raise levels of concurrently administered medications such as certain antihistamines, benzodiazepines, and digoxin.

4. Tricyclic antidepressants

a. Cardiovascular effects

Cardiovascular effects, including arrhythmias, can be problematic with TCA treatment. Consequently, a pretreatment ECG is indicated for patients with significant cardiac risk factors and patients older than age 50 years. Follow-up ECGs may also be indicated to identify the development of conduction changes, typically during the early phase of TCA use (182). Tricyclic antidepressants act similarly to class Ia antiarrhythmic agents such as quinidine, disopyramide, and procainamide, which increase the threshold for excitation by depressing fast sodium channels, prolong cardiac cell action potentials through actions on potassium channels, and prolong cardiac refractoriness through actions on both types of channels (183). As a result, combinations of TCAs with other class I antiarrhythmic agents can exert additive toxic effects on cardiac conduction; patients with ventricular arrhythmias taking another class I antiarrhythmic agent who require TCA therapy should be under careful medical supervision. Individuals with prolonged QT intervals, whether preexistent or medication induced, are predisposed to develop ventricular tachycardia (184). Even patients with normal pretreatment ECG results may develop atrioventricular block with TCAs that reverts to normal after discontinuation of antidepressant medication treatment (185). Because of these effects on cardiac conduction, TCAs (like other class Ia antiarrhythmic agents) may carry an increased risk of serious cardiac adverse effects, including mortality (186–189). In addition, fatal arrhythmias can occur in the context of TCA overdose (190, 191).

In addition to causing arrhythmias, TCAs can cause a number of other cardiovascular side effects, including tachycardia (through muscarinic cholinergic blockade and α-adrenergic blockade) or orthostatic hypotension (through α-adrenergic blockade). Side effects such as orthostatic hypotension may in turn lead to events such as dizziness, falls, or fractures, which are of particular concern in elderly patients (192). Of the TCAs, nortriptyline may be less likely to contribute to orthostatic blood pressure changes (185). Preexisting orthostasis, antihypertensive treatment, dehydration, and salt depletion, whether voluntary or a result of diuretic treatment, may contribute to symptomatic orthostatic hypotension with TCAs. If there is no medical contraindication, patients with symptomatic orthostatic hypotension should maintain adequate fluid intake and be cautioned against extreme dietary salt restriction.

b. Anticholinergic side effects

All TCAs have antimuscarinic effects; tertiary amine tricyclic antidepressants produce the most anticholinergic side effects, whereas the secondary amines desipramine and nortriptyline have less antimuscarinic activity (193). The most common consequences of muscarinic blockade are dry mouth, impaired ability to focus vision at close range, constipation, urinary hesitation, tachycardia, and sexual dysfunction. Although patients can develop some degree of tolerance to anticholinergic side effects, these symptoms may require treatment if they cause substantial dysfunction or interfere with adherence. Impaired visual accommodation may be counteracted through the use of pilocarpine eye drops. Dry mouth may be counteracted by advising the patient to use sugarless gum or candy and ensuring adequate hydration. Constipation can be managed by adequate hydration and the use of bulk laxatives. Antidepressant medications with anticholinergic side effects should be avoided in patients with cognitive impairment, narrow-angle glaucoma, or prostatic hypertrophy. Tricyclic antidepressants can impair memory and concentration and even precipitate anticholinergic delirium, particularly in patients who are elderly, medically compromised, or taking other anticholinergic medicines. Such toxic confusional states may signal the presence of high TCA blood levels and can improve with lowering of the dose (194).

c. Sedation

Tricyclic antidepressants also have affinity for histaminergic receptors and produce varying degrees of sedation. In general, tertiary amines cause greater sedation, while secondary amines cause less (193). Sedation often attenuates in the first weeks of treatment, and patients experiencing only minor difficulty from this side effect should be encouraged to allow some time to pass before changing antidepressant medications. Patients with major depressive disorder with insomnia may benefit from sedation when their medication is given as a single dose before bedtime.

d. Weight gain

Tricyclic antidepressants can cause weight gain, possibly through their histaminergic properties and/or blockade of 5-HT_2 receptors (195). The degree of weight gain appears to vary by agent (e.g., greater weight gain with amitriptyline and less with desipramine), is often dose dependent, and is potentially reversible with cessation of TCA therapy. Regular monitoring of weight permits early detection of weight gain and can allow the treating clinician and patient to determine whether a management plan to minimize or forestall further weight gain is clinically indicated.

e. Neurological effects

Tricyclic antidepressants can cause myoclonus (196). Since this may be a sign of toxicity, the clinician may wish to check the blood level (if available) to ensure that it is not excessive. If the level is nontoxic and myoclonus is not

bothersome to the patient, the agent may be continued without a change in dose. If the myoclonus is problematic and the blood level is within the recommended range, the patient may be treated with clonazepam at a dose of 0.25 mg t.i.d. Alternatively, the antidepressant medication may be changed. In overdoses, TCAs can cause seizures. Some vulnerable patients may experience seizures even on therapeutic doses of a TCA—especially clomipramine and maprotiline (197). Amoxapine, a dibenzoxazepine-derivative tricyclic antidepressant, also produces seizures in overdose and has active metabolites that block dopamine receptors, conferring a risk of extrapyramidal side effects and tardive dyskinesia (198).

f. Falls

Use of TCAs has been associated with an increased risk of falls in a number of studies and meta-analyses, and the relative risk of falling appears comparable to that with SSRI treatment (141, 144, 145). Although systematic reviews show a relatively minor effect of orthostatic hypotension on fall risk, TCAs may contribute to orthostasis and falls in individual patients (153). If orthostatic hypotension is prominent or associated with gait or balance problems, it may require further evaluation and treatment to minimize the likelihood of falls (199). Other aspects of fall risk with TCAs are similar to those that have already been described for patients treated with SSRIs (Section II.B.2.b.1.e). Other causes of falls include bradycardia, cardiac arrhythmia, a seizure, or ataxia.

g. Medication interactions

A number of medications that inhibit, induce, or are metabolized by hepatic microsomal enzymes can interact with TCAs (200). For example, medications that induce CYP 3A4 such as carbamazepine or barbiturates will cause a decrease in serum levels of TCAs. Drugs such as the antipsychotic medication perphenazine or SSRIs such as fluoxetine or paroxetine can inhibit metabolism via CYP 2D6, resulting in a reduced clearance and increased levels of TCAs. Tricyclic antidepressants can also alter the pharmacokinetics or pharmacodynamics of other medications; for example, TCAs can cause a lowering of valproate levels and reduce the activity of clonidine. Therefore, adjustments in medication doses may be necessary when TCAs are administered concomitantly with other drugs for which there is an interaction. The ability to obtain meaningful antidepressant blood levels to guide dosing is an advantage with several of the TCAs (e.g., nortriptyline, amitriptyline, desipramine, imipramine) (201). Potentially dangerous interactions, including hypertensive crises and serotonin syndrome, can develop when TCAs are administered with MAOIs (see Sections II.B.2.b and II.B.2.b.5.b), norepinephrine, or epinephrine.

5. Monoamine oxidase inhibitors

a. Hypertensive crises

A hypertensive crisis can occur when a patient taking an MAOI ingests large amounts of tyramine or other vasoactive amines in foods or medications (202). This reaction is characterized by the acute onset of severe headache, nausea, neck stiffness, palpitations, profuse perspiration, and confusion and can possibly lead to stroke and death (119). Dietary restrictions include avoiding foods such as aged cheeses or meats, fermented products, yeast extracts, fava or broad beans, red wine, draft beers, and overripe or spoiled foods (202, 203). A number of medications including norepinephrine reuptake blocking drugs (e.g., SNRIs, TCAs), sympathomimetic vasoconstrictive agents, and over-the-counter decongestants can also produce a hypertensive crisis when used in combination with MAOIs (202, 204). Individuals with asthma who receive MAOIs should be cautioned regarding interactions with sympathomimetic bronchodilators, although other antiasthma agents appear to be safe. Stimulants may be added to MAOIs, but only with caution and in selected individuals with treatment-resistant symptoms (205, 206).

At low doses (6 mg/24 hours), selegiline differs from the older MAOIs in selectively blocking MAO B. In addition, the transdermal delivery of selegiline bypasses enzyme inhibition in the gut and first-pass metabolism in the liver. As a result, a low-tyramine diet is not needed when selegiline is prescribed at the minimum therapeutic dose. However, few safety data are available at higher doses at which selegiline becomes nonselective and inhibits both MAO A and MAO B. Consequently, a low-tyramine diet is needed when doses of 9 mg/24 hours and higher are prescribed as with other MAOIs (207, 208). Moclobemide, which is available in Canada but not the United States, differs from the above MAOIs in binding reversibly to MAO and makes dietary restrictions unnecessary with moclobemide. The potential for drug-drug interactions with selegiline and moclobemide has not been fully studied, but caution suggests that the same drug interactions should be considered as when prescribing the older, nonselective, irreversible MAOIs.

Although some clinicians continue to recommend that patients carry nifedipine as a self-administered antidote (e.g., 10 mg by mouth at the first sign of a hypertensive crisis [209]), this practice has not been approved by the FDA, and there are concerns about both the safety and efficacy of this strategy, which can produce dangerous hypotension (210). Definitive treatment of hypertensive crises usually involves intravenous administration of an antihypertensive agent (e.g., labetalol, sodium nitroprusside) in an emergency department setting.

b. Serotonin syndrome

As discussed previously in Section II.B.2.b.1.g, serotonin syndrome is caused by excess CNS serotonergic activity and is characterized by abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status changes, tremor and myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and possibly death. Serotonin syndrome most commonly occurs when MAOIs (including reversible inhibitors of monoamine oxidase and selegiline) are taken in close proximity to other serotonergic agents, such as buspirone or antidepressants (157, 204, 211). Consequently, when patients are being changed from an SSRI other than fluoxetine or an SNRI to an MAOI, a waiting period of at least 2 weeks is needed between the discontinuation of one medication and the initiation of the other. When changing from fluoxetine to an MAOI, a waiting period of at least 5 weeks is needed before the MAOI is started (Table 8). Other medications that have been reported to produce serotonin syndrome when used in conjunction with MAOIs include synthetic opioids (e.g., dextromethorphan, meperidine, tramadol, propoxyphene, methadone), nonantidepressant tricyclic compounds (e.g., carbamazepine, cyclobenzaprine), sibutramine, and over-the-counter cold products such as chlorpheniramine (204).

c. Cardiovascular effects

Orthostatic hypotension is commonly seen during MAOI treatment. Possible treatments for this side effect include adding dietary salt to increase intravascular volume, or use of the mineralocorticoid fludrocortisone. Use of MAOIs can also be associated with the development of peripheral edema, which may be helped by the use of support stockings.

d. Weight gain

Weight gain is also commonly seen in patients treated with nonselective MAOIs. Although clinical experience is limited, results of one 52-week study suggested that treatment with transdermal selegiline may not be associated with an increased risk of weight gain (212).

e. Sexual side effects

Sexual side effects seen with MAOI therapy include anorgasmia, decreased libido, and erectile or ejaculatory dysfunction. Sexual side effects may diminish over time or with reductions in MAOI doses. The transdermal formulation of selegiline appears to have a relatively low risk of sexual side effects (213).

f. Neurological effects

Treatment with MAOIs can also be accompanied by headaches and insomnia; these side effects may diminish over time with continued use. Other neurological effects seen with MAOIs include sedation, myoclonic jerks, paresthesias, intense daytime drowsiness, and, rarely, peripheral neuropathy.

c. Implementation of pharmacotherapy

Improvement with pharmacotherapy can be observed as early as the first 1–2 weeks of treatment, and improvement continues up to 12 weeks. Many patients may show partial improvement as early as the end of the first week (214–216). Others achieve improvement within the first 2–4 weeks (217–220). In short-term efficacy trials, all antidepressant medications appear to require at least 4–6 weeks to achieve maximum therapeutic effects (221, 222). There is also evidence for continued accrual of benefit for an additional 4–6 weeks (223). Furthermore, longer time to therapeutic effect has been seen with studies conducted in "real world" settings (224), as well as in studies of patients with more chronic illness (225, 226) or patients with major depressive disorder complicated with co-occurring medical and/or Axis I disorders (224, 227).

Once an antidepressant medication has been selected, it can be started at doses suggested in Table 6. Initial doses should be incrementally raised as tolerated until a therapeutic dose is reached or the patient achieves remission, provided there has been at least some improvement in symptoms in the initial weeks of treatment (217–220). For patients who exhibit a partial response to treatment, doses of antidepressant medications should be maximized, side effects permitting, before changing to a different antidepressant medication. In some instances, due to factors such as rapid metabolism of medication (228, 229), patients may require doses above those noted in FDA labeling. Patients who have achieved some improvement during the initial weeks of treatment should be encouraged to continue taking antidepressant medication for a total of at least 4–8 weeks. If at least moderate improvement is not observed with maximally tolerated doses after 4–8 weeks of treatment, reappraisal and adjustment of the pharmacotherapy should be considered. Patients with no improvement in the initial weeks of treatment generally need an earlier adjustment of treatment. For these patients, the psychiatrist should consider changing to another antidepressant rather than increasing the dose of the medication. For some antidepressant medications, the exact relationships between doses and major depressive disorder symptom response have not been rigorously investigated with fixed-dose studies, and minimum effective doses have not been clearly established; moreover, for other antidepressant medications, some studies have failed to show dose-response relationships (230, 231). Therefore, the initial doses and usual adult doses in Table 6 are intended to serve as general guidelines, and actual doses may vary from individual to individual.

Titration of the dose to full therapeutic doses generally can be accomplished over the initial week(s) of treatment but may vary depending on the development of side effects, the patient's age, and the presence of co-occurring medical and psychiatric conditions. In general, patients who are older, are medically compromised, or have decreased ability to metabolize and clear antidepressant medications will require lower doses. In such patients, reduction of initial and therapeutic doses to 50% of usual adult doses is often recommended, and dose escalations should be made at a slower rate than for younger and healthier adults. Doses will also be affected by the side effect profile of medications and the patient's ability to tolerate these side effects. Medication doses should also be tailored to individual patients depending on the potential for pharmacokinetic alterations and drug-drug interactions.

Patients who have started taking an antidepressant medication should be carefully and systematically monitored to assess their response to treatment, the emergence of side effects, their clinical condition, safety, and adherence to treatment. Use of clinician- and patient-rated scales can facilitate such assessments (see Section II.A.8). Factors to consider when determining the frequency of treatment visits include the severity of illness, the patient's cooperation with treatment, the availability of social supports, the presence of co-occurring general medical illnesses, and the progression of symptom change. Visits should also be frequent enough to monitor and address suicide risk and to actively promote treatment adherence, since attrition from treatment continues to be a major hurdle in maximizing outcomes. Patients in clinical trials appear to benefit from monitoring once a week or more. This frequency of monitoring enhances adherence rates and likely helps patients avoid the demoralization that may occur before the onset of beneficial effects (216). In the recently completed STAR*D ("Sequenced Treatment Alternatives to Relieve Depression") trial, up to six visits were recommended during the first 12 weeks (acute phase) of measurement-based treatment at each of the four treatment steps (40). In clinical practice, the frequency of monitoring during the acute phase of pharmacotherapy may vary and can be as often as multiple times per week in more complex circumstances. The method of monitoring (e.g., face-to-face visits, telephone contact, or contact with another clinician knowledgeable about the patient) may vary depending on the clinical context and the treatment modality.

Although for most patients, monitoring of antidepressant blood levels is not necessary, it may be useful for those taking TCAs. For some medications, particularly nortriptyline, amitriptyline, desipramine, and imipramine, blood drug levels correlate with both efficacy and side effects (201, 232, 233). When such medications are given, obtaining blood drug levels can be particularly informative when patients have not responded to treatment with an adequate dose of antidepressant medication for an adequate duration; when patients are particularly vulnerable to the toxic effects of a medication and require the lowest possible effective dose; when there are concerns about patient adherence; and when there is concern that drug-drug interactions are adversely affecting antidepressant medication levels. In time, genetic testing may help guide selection or dosing of antidepressants, but data are currently insufficient to justify the cost of such tests (229).

Some antidepressant medications, especially TCAs, can cause significant morbidity and mortality in overdose (190, 191). Ingestion of a 10-day supply of a tricyclic agent administered at a dose of 200 mg/day is often lethal. Early on in treatment, it is prudent to dispense only small quantities of such antidepressant medications and keep in mind the possibility that patients can hoard medications over time. Alternatively, in patients who are suicidal, it may be preferable to employ agents that are safer in overdose such as the SSRIs, bupropion, or mirtazapine.

3. Other somatic therapies

a. Electroconvulsive therapy

Electroconvulsive therapy has the highest rates of response and remission of any form of antidepressant treatment, with 70%–90% of those treated showing improvement (234–236). Although the remission rate with ECT appears to be lower when it is used in community settings than when it is used in clinical trials (237), the proportion of patients with major depressive disorder who respond to ECT is still greater than the proportion who respond to antidepressant medication. In addition, ECT has been associated with significant improvements in health-related quality of life (238). Consequently, ECT should be considered for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly those with significant functional impairment who have not responded to numerous medication trials (239). Electroconvulsive therapy may be particularly beneficial and can be considered as a first-line treatment option for severe major depressive disorder when it is coupled with psychotic features (240, 241), catatonia (239, 242), suicide risk (243), or food refusal leading to nutritional compromise, as well as in other situations when a particularly rapid antidepressant response is required (240), such as with severely ill inpatients (239). Electroconvulsive therapy is also indicated as a first-line treatment for patients who have previously shown a positive response to this treatment modality or who prefer it (239).

1. Side effects of electroconvulsive therapy

Electroconvulsive therapy is a very safe treatment, and there are no absolute contraindications to its use (239). Risks of morbidity and mortality, in general, do not exceed those associated with anesthesia alone (239, 244, 245). However, the presence of some medical conditions may necessitate modifications in anesthesia or ECT administration.

Electroconvulsive therapy may have cardiovascular side effects, mediated by changes in the autonomic nervous system with the initial stimulus and subsequent seizure activity (239). More specifically, ECT typically causes a transient rise in heart rate and blood pressure, with associated increases in cardiac workload and intracranial pressure. These effects can be managed by optimizing blood pressure control prior to ECT and administering antihypertensive agents (e.g., short-acting beta-blockers or calcium channel blockers) at the time of ECT (239). Arrhythmias, which are usually transient, can also occur in conjunction with ECT and can be managed with usual antiarrhythmic therapies if they do not resolve spontaneously (239).

Electroconvulsive therapy can also be associated with cognitive effects, the most common of which is a period of confusion following the ECT and associated anesthesia that generally lasts between 30 and 60 minutes (246). Electroconvulsive therapy also is associated with anterograde amnesia, which typically resolves soon after the last ECT treatment (247). Some degree of retrograde amnesia, particularly for recent memories, may continue for a longer period of time after the end of the ECT course (247) but is less pronounced for autobiographical memories than for impersonal memories (248). These cognitive effects of ECT are related to electrode placement, stimulus dosage, age, and premorbid cognitive status (249–253). Retrograde amnesia also improves over time, typically resolving within 6 months (248, 252), although some patients report incomplete recovery of memories, particularly for events around the time of the treatment (247, 254). Rarely, patients report more pervasive and persistent cognitive disruption, the basis of which is uncertain (252, 255). For many individuals, however, subjective memory (256) and quality of life (238) is improved following ECT with the resolution of the major depressive episode and its associated deficits in memory or executive functioning (257, 258).

2. Implementation of electroconvulsive therapy

The evaluation preceding ECT consists of a psychiatric history and examination to verify that ECT is indicated, a general medical evaluation (including medical history and physical examination with cognitive assessment, vital signs, and any specifically indicated laboratory, radiologic, or imaging studies) to define factors that may influence the risk of ECT, and an anesthesia evaluation to identify and address the nature and extent of anesthetic risk and the need for modification of medications or anesthetic technique (239). This evaluation should include a summary of treatment indications, treatment risks, and a suggestion of any indicated additional evaluative procedures, alterations in treatment, or modifications in ECT technique (239). In assessing indications for caution (e.g., recent myocardial infarction, cardiac arrhythmias, intracranial space-occupying lesions), the relative risks and benefits should be carefully weighed in collaboration with an anesthesiologist, a general medical physician, and other specialists, as necessary. Once completed, the pre-ECT evaluation will serve as the basis for a specific, individualized discussion of the risks and benefits of ECT relative to other therapeutic options as part of the informed consent process. With the patient's permission, it is helpful to educate the patient's family about ECT and involve them in discussions relating to consent.

An additional aspect of decision-making prior to ECT relates to the use of psychotropic medications during the ECT course. There is growing use of ECT combined with antidepressant medication. Although data supporting this practice are still few, it does not appear to increase side effects and may augment response (259, 260). An additional goal of combination treatment is to minimize the risk of relapse between the end of the ECT course and the attainment of full antidepressant effectiveness. Antipsychotic medications are typically continued during the ECT course (239, 261), although most data on this practice come from studies of patients with schizophrenia who are receiving ECT. The safety of combining lithium and ECT has been questioned, although there are conflicting data (239, 262). Medications that have anticonvulsant properties are often discontinued or given at decreased doses during the ECT course to minimize effects on seizure induction (239, 261). With benzodiazepines, there is some evidence that concurrent use may diminish ECT effectiveness, particularly when right unilateral electrode placement is used (263).

Electroconvulsive therapy may be administered either unilaterally or bilaterally (using a bitemporal or bifrontal electrode placement). Compared with patients who receive bilateral treatment, most patients who receive right unilateral electrode placement with low stimulus intensities experience fewer cognitive effects but less therapeutic benefit (253). Stimuli of higher intensity (i.e., 500% above seizure threshold) are associated with antidepressant effects more comparable to those seen with bilateral electrode placements, although such stimulus intensities are

not always achievable with existing ECT devices (264). Regardless of what electrode placement is chosen, stimulus dosing should be individualized and stimulus parameters adjusted to induce an adequate generalized seizure, which is typically at least 20 seconds or greater in motor duration and 30 seconds in EEG duration (239). Failure to induce an adequate seizure should be followed immediately by restimulation at higher energies until an adequate seizure is elicited.

Electroconvulsive therapy is typically administered 2–3 times/week; less frequent administration has been associated with less cognitive impairment but also a longer lag in the onset of action (265). In clinical practice, the need for ECT to be administered at this frequency could produce logistical barriers for some patients who would either require hospitalization or transportation after ECT sessions. The acute course of ECT treatment typically consists of six to 12 treatments and generally does not exceed 20 treatments (239, 266). It is important that treatment continue until symptoms have remitted or clearly reached a plateau, since relapse rates appear to be greater and overall prognosis worse if ECT is discontinued prematurely (237). Use of a formal rating scale may be helpful in assessing symptom response as well as the cognitive side effects of treatment, permitting adjustments in the treatment parameters or frequency (239, 267).

For more detail on the administration of ECT, see APA's *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging (A Task Force Report of the American Psychiatric Association)* (239).

b. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses a specifically designed magnetic coil that is placed in contact with the head to generate rapidly alternating magnetic-resonance-imaging-strength magnetic fields and produce electrical stimulation of superficial cortical neurons. Based on the results of a multisite randomized sham-controlled clinical trial of high-frequency TMS over the left dorsolateral prefrontal cortex (268), TMS was cleared by the FDA in 2008 for use in individuals with major depressive disorder who have not had a satisfactory response to at least one antidepressant trial in the current episode of illness. However, another large randomized sham-controlled trial of TMS added to antidepressant pharmacotherapy showed no significant benefit of left dorsolateral prefrontal cortex TMS (269). In comparisons of actual TMS versus sham TMS, most (270–272) but not all (273) recent meta-analyses have found relatively small to moderate benefits of TMS in terms of clinical response. Although the primary studies used in these meta-analyses are highly overlapping and the variability in TMS stimulus parameters and treatment paradigms complicates the interpretation of research findings, these meta-analyses also support the use of high-frequency TMS over the left dorsolateral prefrontal cortex. Lesser degrees of treatment resistance may be associated with a better acute response to TMS (274).

In comparison with ECT, TMS has been found in randomized studies to be either less effective than ECT (275) or comparable in efficacy to ECT (276–278), but in the latter studies TMS was more effective and ECT was less effective than is typically seen in clinical trials. A fewer number of studies have compared cognitive effects of TMS and ECT. One randomized trial found no significant difference between TMS and non-dominant unilateral ECT on performance on neuropsychological tests at 2 and at 4 weeks of treatment (276), although a small open-label trial reported a greater degree of memory difficulties with ECT than with TMS shortly after the treatment course (279).

Across all studies, TMS was well tolerated and was associated with low rates of treatment dropout (270, 280). Transient scalp discomfort and headaches were the most commonly reported side effects (280).

In clinical practice, the need for daily TMS could produce logistical barriers for some patients.

c. Vagus nerve stimulation

Vagus nerve stimulation is approved for use in patients with treatment-resistant depression on the basis of its potential benefit with long-term treatment. There is no indication for the use of VNS in acute phase treatment of depression, as data showed no evidence for acute efficacy (281, 282). Further information on the use of VNS as an adjunct to other antidepressive treatments is provided in Section II.B.7.c.

4. Psychotherapy

There has been considerable research on time-limited psychotherapies for major depressive disorder, although the number of studies is smaller than for pharmacotherapies. Most research has focused on individual, in-person, outpatient treatment, in part based on the needs and constraints of research methods. However, research has also begun to explore psychotherapies in differing formats, including groups, over the telephone, and with computer assistance.

When psychotherapy is part of the treatment plan, it must be integrated with psychiatric management (Section II.A) and any other treatments (e.g., pharmacotherapy) that are being provided. Clinical considerations and other patient factors should be considered in determining the nature and intensity of psychotherapy. Typically psychotherapy is given in an ambulatory setting, although some

psychotherapies might benefit depressed inpatients, given adequate lengths of stay and courses of treatment (283–285). Like pharmacotherapy, the effectiveness of psychotherapy will vary with the skill and training of the therapist. Patient factors, such as the nature and duration of depressive symptoms, beliefs and attitudes toward psychotherapy, and early life experiences (e.g., history of trauma) also affect treatment response to psychotherapy. Psychotherapy is particularly useful in addressing the psychosocial stressors and psychological factors that have an impact on the development or maintenance of depressive symptoms.

Cognitive-behavioral therapy, interpersonal psychotherapy (IPT), and behavioral psychotherapies (e.g., behavioral activation) have demonstrated acute efficacy in treating major depressive disorder. There is less evidence for other psychotherapies. However, one meta-analysis found no large differences in long-term efficacy between any of the major psychotherapies, including dynamic psychotherapy, for mild and moderate depression (286). In terms of longer term outcomes, psychotherapy is generally found to have more prolonged effects than pharmacotherapy after cessation of active treatment. In particular, IPT and CBT have shown lasting benefits in maintaining remission (287–289). These time-limited treatments are essentially equipotent with antidepressant medications for outpatients with mild to moderate acute depression but probably should be used in conjunction with medication for severe or melancholic major depressive disorder. Some research has suggested patient and illness characteristics that might predict differential benefits of CBT over IPT, and vice versa, for patients with major depressive disorder (e.g., see reference 290), but such preliminary findings require replication.

Cognitive-behavioral therapy and IPT appear less effective than pharmacotherapy for chronic depression, at least as acute monotherapy (291–296). Nonetheless, in patients who respond to medication, psychotherapy may foster the development of social skills and confidence after years of depression-related impairments (297).

Psychotherapy carries its own "side effects." A psychotherapy that requires considerable time or patience may be poorly tolerated. The work of psychotherapy itself may generate anxiety or other strong feelings, which may be difficult for patients to manage. An indirect measure of the relative side effects and tolerability of psychotherapy can be obtained from the dropout rates in clinical trials; however, many other factors can also affect these rates (e.g., other burdens of the research trial, specific features of the clinical management provided, logistical barriers in attending appointments). Depending on what can reasonably be expected with the given type of psychotherapy, the psychiatrist should consider a change in the intensity or type of psychotherapy and/or addition or change to medication if psychotherapy for major depressive disorder has not resulted in significant improvement in 4–8 weeks.

a. Specific psychotherapies

1. Cognitive and behavioral therapies

In the treatment of depressed patients, psychotherapies that focus primarily on aspects of cognitive patterns and those that emphasize behavioral techniques can be used alone, but are generally used in combination. Cognitive-behavioral therapy combines cognitive psychotherapy with behavioral therapy and maintains that irrational beliefs and distorted attitudes toward the self, the environment, and the future perpetuate depressive affects and compromise functioning. The goal of CBT is to reduce depressive symptoms by challenging and reversing these beliefs and attitudes and encouraging patients to change their maladaptive preconceptions and behaviors in real life (298).

Cognitive-behavioral therapy is an effective treatment for major depressive disorder. In meta-analyses, CBT has generally surpassed control conditions in efficacy and has had equal efficacy compared with other empirically supported psychotherapies (i.e., IPT and behavior therapy) (299). Studies comparing the effectiveness of CBT with pharmacotherapy, however, are methodologically challenging to conduct, and results are inconsistent (296, 300). Also unclear is whether CBT is less effective for patients with more severe depressive symptoms.

Behavior therapy for major depressive disorder is based on theoretical models drawn from behavior theory (301) and social learning theory (302). Behavioral activation is a newly articulated behavioral intervention with some positive preliminary results that merit further study (288, 303). Specific behavior therapy techniques include activity scheduling (304, 305), self-control therapy (306), social skills training (307), and problem solving (308). Behavior therapy involves graded homework, scheduling of enjoyable activities, and minimizing unpleasant activities (309). Behavior therapy has demonstrated efficacy, at times superior to cognitive therapy, in treating major depressive disorder (310).

2. Interpersonal psychotherapy

The focus of IPT is on current life changes, including losses, role disputes and role transitions, social isolation, deficits in social skills, and other interpersonal factors that may interact with the development of the depressive episode (311, 312). In IPT the goal is to intervene by identifying the current trigger of the depressive episode, facilitating mourning in the case of bereavement, promoting recognition of related affects, resolving role disputes and

role transitions, and building social skills to improve relationships and to acquire needed social supports. In IPT, major depressive disorder is defined as a medical illness, and the illness, rather than the patient, is blamed for the symptoms. Interpersonal psychotherapy's medical model makes it highly compatible with pharmacotherapy in combined treatment.

Interpersonal psychotherapy is an efficacious treatment for major depressive disorder (296, 313). Studies have shown efficacy of this treatment in depressed primary care patients and patients with more severe depression (311). The efficacy of IPT has been demonstrated for adolescents, pregnant and postpartum women, and geriatric patients (311). Interpersonal psychotherapy can also be used as a monthly maintenance therapy to prevent relapse (289, 314, 315). Some studies have also suggested possible subgroups in whom IPT may show differential efficacy, specifically among HIV-positive patients (316) and patients who have co-occurring obsessive personality traits and who are single and not living with others (317). Furthermore, for patients with severe life events, IPT may have advantages over therapies that do not focus on such events directly.

3. Psychodynamic psychotherapy

The term "psychodynamic psychotherapy" encompasses a range of brief to long-term psychotherapeutic interventions (318–320). These interventions derive from psychodynamic theories about the etiology of psychological vulnerability, personality development, and symptom formation as shaped by development and conflict occurring during the life cycle from earliest childhood forward (321–325). Some of these theories focus on conflicts related to guilt, shame, interpersonal relationships, the management of anxiety, and repressed or unacceptable impulses. Others address developmental psychological deficits produced by inadequacies or problems in the relationship between the child and emotional caretakers, resulting in problems of self-esteem, sense of psychological cohesiveness, and emotional self-regulation (323, 326–330).

Psychodynamic psychotherapy may be brief but usually has a longer duration than other psychotherapies, and its aims extend beyond immediate symptom relief. These goals are to modify underlying psychological conflicts and deficits, which increase the patient's vulnerability to depressive affect and the development of major depressive disorder. Psychodynamic psychotherapy is therefore broader than most other psychotherapies, encompassing both current and past problems in interpersonal relationships, self-esteem, and developmental conflicts associated with anxiety, guilt, or shame. Time-limited, structured psychodynamic psychotherapy may focus more on understanding the psychological basis of the presenting symptoms or on a selected underlying conflict. Sometimes a goal of psychodynamic psychotherapy, brief or extended, may be to help the patient accept or adhere to necessary pharmacotherapy (331).

Although psychodynamic psychotherapy is often used in clinical practice, its efficacy in the acute phase of major depressive disorder remains less well studied in controlled trials than the efficacy in this phase of some other forms of psychotherapy. This research is reviewed in Part B, Section V.B.3.

4. Problem-solving therapy

Problem-solving therapy is a manual-guided, brief treatment lasting six to 12 sessions. This therapy, often administered by nurses or social workers, has been used to prevent depression in elderly and/or medically ill patients, and it has also been used to treat patients with relatively mild depressive symptoms. The approach combines elements of cognitive therapy (addressing negative assessments of situations) and IPT (focal problem solving). Some studies have reported modest improvement in patients with mild depressive symptoms. Although problem solving therapy has had limited testing for patients with major depressive disorder, it may have a role in targeted patient populations with mild depression (332–335).

5. Marital therapy and family therapy

Marital and family problems are common in the course of mood disorders, and comprehensive treatment often demands assessing and addressing these problems. Marital and family problems may be the consequence of major depressive disorder but may also increase vulnerability to developing major depressive disorder or retard recovery from it (336–339). A number of marital and family therapies have been shown to be effective in the treatment of depression. Techniques include behavioral approaches (338), problem-focused approaches (340), and strategic marital therapy (341, 342). Family therapy has also been found to be helpful in the treatment of more severe forms of depression in conjunction with medications and hospitalization (343).

6. Group therapy

Group psychotherapy is widely practiced, but research on its application to major depressive disorder is limited. Specific types having some data to support their efficacy include CBT (344–347) and IPT (348–351). Meta-analyses of the relative effectiveness of psychotherapeutic approaches conducted in group format versus individual format have not involved patients with rigorously defined major depressive disorder (352–355).

On the basis of a very limited controlled study, supportive group therapy has been suggested to have utility in the treatment of major depressive disorder. In a study of depressed outpatients, a mutual support group and group CBT were found to be equally effective in reducing depressive symptoms (346). In a study of HIV-positive patients with mild to moderate major depressive disorder, structured supportive group therapy plus placebo yielded similar decreases in depressive symptoms to structured group therapy plus fluoxetine (356). Individuals experiencing stressors such as bereavement or chronic illness may benefit from contact with others facing similar challenges.

Medication maintenance support groups may also offer benefits, although data from controlled trials for patients with major depressive disorder are lacking. Such groups inform the patient and family members about prognosis and medication issues, providing a psychoeducational forum that contextualizes a chronic mental illness in a medical model.

The efficacy of self-help groups led by lay members (357) in the treatment of major depressive disorder has not been well studied. However, one investigation of group therapies found that a higher proportion of depressed outpatients had remission following treatment in groups led by professionals than had remission following participation in groups led by nonprofessionals (346). Further study is needed on the possibility that self-help groups may serve a useful role in enhancing the support network and self-esteem of participating patients with major depressive disorder and their families.

Overall, group therapy has some evidence to support its use as well as the potential advantage of lowered cost, inasmuch as one or two therapists can treat a larger number of patients simultaneously. This advantage needs to be weighed against the difficulties in assembling the group, the lesser intensity of focus patients receive relative to individual psychotherapy, and potentially adverse effects from interactions with other group members.

b. Implementation

It can be useful to establish an expected duration of psychotherapy at the start of treatment. Communicating this expectation may help mobilize the patient and focus treatment goals, yet there are few data available on the optimal duration of specific depression-focused psychotherapies. In many trials, CBT and IPT have been delivered in approximately 12–16 weekly sessions. In a subanalysis of one clinical trial, CBT delivered in 16 weeks was more effective than CBT delivered in 8 weeks for those with severe major depressive disorder (358). Moreover, evidence suggests benefit from monthly continuation phase treatment with IPT in reducing the probability of relapse (314). In addition, patients with chronic, treatment-resistant depression may require long-term treatment.

The optimal frequency of psychotherapy has not been rigorously studied in controlled trials. The psychiatrist should consider multiple factors when determining the frequency for individual patients, including the specific type and goals of the psychotherapy, the frequency necessary to create and maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, and the frequency necessary to monitor and address suicide risk and other safety concerns. Time-limited brief psychotherapies may mobilize many depressed patients to more rapid improvement. The severity of illness, the patient's cooperation with treatment, availability of social supports, cost, geographic accessibility, and presence of co-occurring general medical problems may also influence visit frequency. The frequency of outpatient visits during the acute phase is generally weekly but may vary based on these factors. Some experienced clinicians find that sessions are needed at least twice weekly, at least initially, for patients with moderate to severe depression.

Regardless of the type of depression-focused psychotherapy that is selected, the clinician should carefully and systematically monitor the patient's response to treatment, which can be facilitated by the use of clinician- and patient-rated scales at regular intervals (see Section II.A.8). If 4–8 weeks of treatment do not yield at least moderate improvement (≥20% diminution in symptoms), the clinician should thoroughly review and reappraise the treatment plan.

c. Combining psychotherapy and medication

Several meta-analyses of studies of the combination of psychotherapy and pharmacotherapy for patients with major depressive disorder have documented a modest advantage for the combination as compared with one or the other modality alone (359–361). Particularly large additive effects have been observed in individual studies of patients with chronic depression (362), patients with severe recurrent depression (359), and hospitalized patients (285). Combined treatment might therefore be considered a treatment of first choice for patients with major depressive disorder with more severe, chronic, or complex presentations. Combining family therapy with pharmacotherapy has also been found to improve posthospital care for depressed patients (343).

Dual treatment combines the unique advantages of each therapeutic modality: while pharmacotherapy may provide earlier symptomatic relief, psychotherapy yields broader and longer lasting improvement (363). Psychotherapy can also be used to address issues that arise during pharmacotherapy, such as decreased adherence. However, the advan-

tage of routinely combining interventions may be modest for patients with less severe depressive symptoms (359).

There are no empirical data from clinical trials to help guide the selection of particular antidepressant medications and particular models of psychotherapeutic approaches for individuals who will receive the combination of both modalities. In general, the same issues that influence these decisions when choosing a monotherapy will apply, and the same doses of antidepressant medication and the same frequency and course of psychotherapy should be used for patients receiving combination modality treatments as are used for patients receiving them as a monotherapy.

Results from a series of recent studies provide indirect evidence that for patients who have had only a partial response to pharmacotherapy, adding a course of CBT may be an effective strategy for preventing relapse (363–368). During 12 weeks of treatment in the STAR*D study, cognitive therapy was as effective as either augmenting with bupropion or buspirone or changing antidepressants to bupropion, sertraline, or venlafaxine. However, patients who did not respond to an initial course of citalopram were less likely to accept cognitive therapy as a change or augmentation option than they were to accept a different medication option (369), perhaps due to the nature of the study design.

5. Complementary and alternative treatments

As defined by the National Center for Complementary and Alternative Medicine, complementary and alternative medicine is "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." As the definitions are usually applied, "complementary" therapies are used conjunctively with conventional medicine, "alternative" therapies are used in place of conventional medicine, and "integrative" medicine makes use of all therapies appropriate to an individual patient's needs.

The use of integrative therapies is increasingly common, although training and comfort with complementary and alternative modalities vary greatly by practitioner. Many patients do not spontaneously disclose use of complementary or alternative treatments to health care professionals, so it is particularly important that direct inquiry about such treatments be part of routine health care questions. At this time, there are several modalities that have modest evidence for antidepressant efficacy and deserve further study. Some of these modalities can be recommended with enthusiasm for their general health benefits; however, patients should be informed that evidence for their antidepressant efficacy as monotherapy is limited or absent.

a. St. John's wort

St. John's wort is a plant widely used to treat depressive symptoms. Overall, studies of St. John's wort show greater consensus and support for benefits in mild to moderate major depressive disorder, as compared with less consistent findings in patients with more severe symptoms. One review of 14 short-term, double-blind trials conducted in outpatients with mild to moderate symptoms of major depressive disorder concluded that St. John's wort in doses of 300 mg/day and 1,800 mg/day had efficacy that was superior to placebo (105). St. John's wort had generally comparable efficacy and fewer side effects than low-dose TCA treatment (e.g., 30–150 mg/day of amitriptyline) (105), but doses at the low end of this range would not be expected to produce therapeutic benefits. However, in the two largest controlled studies conducted in the United States (370, 371), effects of St. John's wort did not differ from placebo, which somewhat limits confidence in the magnitude of the antidepressant actions of St. John's wort. In addition, preparations of St. John's wort are not regulated by the FDA as a drug and lack standardization of their ingredients, composition, and potency. Based on the evidence cited, St. John's wort would not meet the FDA's minimum requirements to be declared an effective antidepressant and is not recommended for general use in treating depression.

Another important consideration with St. John's wort is the potential for drug-drug interactions (372–374). St. John's wort appears to induce the metabolism of drugs via CYP 3A4, reducing the efficacy of medications, including antiretroviral medications, immunosuppressants (including cyclosporine), antineoplastic agents, anticoagulants (including warfarin), oral contraceptives, and hormone replacement therapy (373, 374). Unwanted pregnancies have been reported with concomitant St. John's wort and oral contraceptive use (373, 375, 376), and rejection of transplanted organs has been observed when St. John's wort is taken concurrently with cyclosporin (374). The significant decreases in antiretroviral medication levels with concomitant St. John's wort use suggest that these medications will be less effective in treating HIV infection (374). Effects of St. John's wort on P-glycoprotein have also been observed, altering the pharmacokinetics and pharmacodynamics of medications such as digoxin that are transported by this route (374). Apart from affecting blood levels of nonpsychiatric medications, the safety and efficacy of the combined use of St. John's wort with other antidepressant medications is not known. The combined use of St. John's wort with MAOIs is contraindicated.

b. *S*-adenosyl methionine

S-adenosyl methionine is a naturally occurring molecule. In humans, it is concentrated in the liver and the brain and

serves as a methyl donor in the synthesis of biologically active compounds such as phospholipids, catecholamines, and the neurotransmitters dopamine and serotonin (377). Cerebrospinal fluid levels of SAMe are lower in individuals with severe major depressive disorder, compared with control subjects (378), and treatment with SAMe increases CSF SAMe and 5-hydroxyindoleacetic acid levels (379). *S*-adenosyl methionine is available for both parenteral and oral administration (380).

Some data support the efficacy and tolerability of SAMe in patients with major depressive disorder. Oral, intravenous, and intramuscular formulations have been assessed and appear efficacious in at least pilot studies (381–383). Like St. John's wort, SAMe is not regulated by the FDA and lacks standardization of its composition and potency. *S*-adenosyl methionine has been compared with TCAs and has been reported to have greater efficacy while being more tolerable (381). It is unclear at present how SAMe compares to SSRIs in efficacy and cost-efficiency. While some data support the use of SAMe as monotherapy and as augmentation therapy, the data at this time, as with St. John's wort, are insufficient to make a recommendation for its use in the treatment of major depressive disorder.

c. Omega-3 fatty acids

Most studies of omega-3 fatty acids for major depressive disorder have been adjunctive studies, in which patients were already receiving antidepressant medications but still met the criteria for major depressive disorder. Studies vary in the omega-3 fatty acids used (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], or the combination), and doses and durations of study trials have also varied. It is difficult to interpret the literature on this treatment given the heterogeneity in study design and outcomes.

Omega-3 fatty acids are generally recommended as an adjunctive therapy for mood disorders, as health benefits, including those for cardiovascular health, are well established, and individuals with psychiatric disorders may be at greater risk for obesity, metabolic problems, and other health problems than the general population (384, 385). More evidence is required to establish a definitive role in the acute treatment of major depressive disorder. Doses of 1–9 grams have been studied in mood disorders, with a majority of evidence supporting use of lower doses. Adjunctive EPA or the combination of EPA and DHA (the combination found in most commercially available brands) appears most useful, with less evidence for DHA alone for the treatment of major depressive disorder. Further data are needed to ascertain the role of omega-3 fatty acids as monotherapy for major depressive disorder.

d. Folate

Folate has been primarily assessed as a predictor of antidepressant medication response and as an adjunctive treatment. Low folate blood levels have been associated with lack of response and slower response to fluoxetine for major depressive disorder (386, 387), and higher folate levels at treatment baseline appear associated with better response to antidepressants (388). Folate has been studied as an adjunctive treatment compared with placebo in addition to fluoxetine, with significantly greater improvement in those receiving folate, especially among female patients (389).

Folate is a low-risk intervention with general health benefits. Folate protects against neural tube defects in early pregnancy. In general, 0.4–1 mg of folate is recommended for women of reproductive age. Considering the modest evidence that supports folate as an augmentation strategy and its attractive risk-benefit profile, folate can be recommended as a reasonable adjunctive strategy for major depressive disorder that carries little risk and may decrease birth defects in the case of pregnancy. Data are inadequate to suggest efficacy as a monotherapy.

e. Light therapy

Bright light therapy appears effective for seasonal affective disorder and nonseasonal major depressive disorder, as demonstrated in generally short-term, placebo-controlled trials (390–394), although some studies have methodological limitations (395). The mechanism of action for light therapy is not clear but appears to involve the serotonergic neurotransmitter system (396, 397). There is some evidence that light therapy may hasten the response to treatment with antidepressant medication (398). Open-label data also support light therapy for patients with major depressive disorder that has not responded to antidepressant medication (399). Greater intensity of light is associated with efficacy (400). Light therapy also may augment the antidepressant benefits of partial sleep deprivation (401, 402). Monitoring for mania and hypomania may be appropriate with initiation of light therapy, as hypomania has been reported (392). However, in general bright light therapy is a low-risk and low-cost option for treatment.

f. Acupuncture

Acupuncture is a treatment modality that is part of traditional Chinese medicine. Its efficacy is somewhat difficult to assess, as much of the research is published in Asian languages and overlooked in typical literature searches. In addition, there is significant variation in the acupuncture techniques used as well as limited descriptions of methodology and diagnosis (403). One randomized trial showed

comparable benefits of electroacupuncture and amitriptyline (404), and another small randomized trial in depressed women showed benefits of acupuncture relative to a sham control (405). However, a subsequent larger study did not replicate these results (406), and a recent meta-analysis concluded that acupuncture was not associated with any benefits in treating major depression in terms of response or remission rates (407). Assuming needles are properly sterilized, there do not appear to be substantial risks of acupuncture treatment. However, based on current evidence, acupuncture is not recommended in the treatment of major depressive disorder.

6. Assessing response and adequacy of treatment

The goal of acute phase treatment for major depressive disorder, insofar as possible, is to achieve remission and a return to full functioning and quality of life. Remission is defined as at least 3 weeks of the absence of both sad mood and reduced interest and no more than three remaining symptoms of the major depressive episode (408). However, it is not uncommon for patients to have substantial but incomplete symptom reduction or improvement in functioning during acute phase treatment. A number of studies have provided compelling evidence that even mild residual symptoms at the end of a depressive episode are associated with significant psychosocial disability, compared with asymptomatic remission (409); a more than three times faster relapse to a subsequent major depressive episode (410); and in first-episode patients, a more chronic future course (410–412). The presence of mild residual symptoms has been shown to be an even stronger predictor of a subsequent return to a major depressive episode than a prior history of multiple episodes of major depressive disorder (410). For this reason, it is important not to conclude the acute phase of treatment prematurely for partially responsive patients. Throughout treatment, both the patient's response and the adequacy of treatment must be vigilantly and systematically monitored. Use of structured measures of depression symptom severity, side effects, treatment adherence, and functional status can facilitate identification of patients who have not had a complete response to treatment (40, 44).

If a patient is found to have an incomplete treatment response, the treatment itself should be evaluated. Medications must be thoughtfully selected and given at an adequate dose and for an adequate duration. Similarly, psychotherapy must be well chosen for the patient, skillfully executed, and conducted over an appropriate period of time with an adequate frequency of visits. In addition to being caused by inadequate treatment, poor response may result from multiple other factors (413) that are enumerated in Table 9.

TABLE 9. Potential Reasons for Treatment Nonresponse

Inaccurate diagnosis
Unaddressed co-occurring medical or psychiatric disorders, including substance use disorders
Inappropriate selection of therapeutic modalities
Inadequate dose of medication or frequency of psychotherapy
Pharmacokinetic/pharmacodynamic factors affecting medication action
Inadequate duration of treatment
Nonadherence to treatment
Persistent or poorly tolerated side effects
Complicating psychosocial and psychological factors
Inadequately trained therapist or poor "fit" between patient and therapist

For pharmacotherapy, determination of the adequacy of treatment requires ensuring that antidepressant medications have been used for an adequate dose and duration. This can be assessed using standardized measurement instruments (414). Generally, adequate treatment with an antidepressant medication for at least 4–6 weeks is necessary before concluding that a patient is not responsive or only partially responsive to a particular medication (218, 221). For patients with no improvement in symptoms during the initial weeks of treatment, treatment should be reevaluated and possibly changed. Furthermore, there is little evidence to support extending antidepressant medication trials beyond 6 weeks in patients who have shown no response. Patients with chronic forms of depression or with co-occurring Axis I disorders or general medical conditions may require a longer duration of acute phase treatment before concluding that a different treatment strategy is indicated (224).

For psychotherapy, treatment should be reassessed if there has not been meaningful improvement after a few months, depending on what can reasonably be expected for the given type of psychotherapy. Patients should be reassessed every 3–4 months to ensure adequate improvement. Regardless of treatment modality, lack of improvement over time warrants reconsideration of interventions, given the large number of available treatment options.

7. Strategies to address incomplete response

The psychiatrist should consider a change in treatment for patients who have not fully responded to an adequate acute phase treatment over a sufficient time, generally 4–8 weeks. The treatment plan can be revised by implementing one of several therapeutic options, including op-

	Response	
	None or Partial	Full
Initial weeks	Assess adherence. If clinical severity warrants and treatment is well tolerated, consider increasing medication dosage or intensity of psychotherapy, especially if there is no response. If symptoms are severe or life-threatening, consider ECT.	If treatment is well-tolerated, maintain current treatment approach.
At 4–8 weeks	In patients treated with an antidepressant, consider increasing the dose (if well tolerated), changing to a different antidepressant, and changing to or augmenting with psychotherapy. Augmentation therapy or ECT may also be considered. For insufficient response to psychotherapy, consider changing the intensity or type of psychotherapy and/or adding or changing to medication. For ECT, see guideline text.	Go to continuation phase.
Throughout treatment	In patients who have significant side effects with antidepressant treatment, consider changing to a different antidepressant, reducing the dose, or treating the side effect. Also consider changing to psychotherapy or ECT. If trials of two medications from the same antidepressant class have been ineffective, consider changing antidepressants to a different class. For patients with difficulty tolerating psychotherapy, consider changing the intensity or type of therapy and/or adding or changing to medication.	

FIGURE 2. Assessment of Treatment Tolerability and Adequacy of Response

timizing the initial treatment, changing to a different treatment, and combining treatments. These options are outlined in Figure 2 and described in more detail below.

Following any change in treatment, the patient should continue to be closely monitored. If there is not at least a moderate improvement in major depressive disorder symptoms after an additional 4–8 weeks of treatment, the psychiatrist should conduct another thorough review. This reappraisal should include the following: verifying the patient's diagnosis and adherence; uncovering and addressing clinical factors that may be preventing improvement, such as the presence of co-occurring general medical conditions or psychiatric conditions (e.g., alcohol or substance abuse); evaluating for potential drug-drug interactions; obtaining collateral information from those involved with the patient; and uncovering and addressing psychosocial, psychological, and personality factors that may be impeding recovery (Table 9). If no new information is uncovered to explain the patient's lack of adequate response, other treatment options should be considered, including ECT and a consultation from an expert in mood disorders. Despite optimal treatment, some patients may continue to have chronic depressive symptoms. For these patients, the psychiatrist should add a disease management component to the overall treatment plan. This component involves setting realistic expectations, improving functioning, and developing self-management skills (415, 416).

a. Maximizing initial treatments

For patients who have not fully responded to treatment for depression, an initial strategy is to optimize the intensity of psychotherapy or maximize the dose of medication, especially if the upper limit of the antidepressant dose has not been reached. Decisions about pharmacotherapy will involve a balancing of efficacy, side effects, and medication adherence. Dose escalation and management of side effects at critical decision points are essential in order to avoid premature discontinuation of the chosen antide-

pressant medication and to maximize the dose and duration of the antidepressant therapy (40, 218).

Because of pharmacokinetic and pharmacodynamic differences among individuals, some patients may require doses higher than those approved by the FDA to achieve adequate blood levels of a medication and receive therapeutic benefits. Patients who have had their dose increased should be monitored for increased severity of side effects; dose increases should be considered only for patients who do not have significant or intolerable side effects while taking the medication. Frequent follow-up contact (either in person or via the phone) may be necessary to address symptoms, side effects, and patient adherence in order to personalize treatment to the specific clinical needs of the patient. When available and clinically meaningful, therapeutic ranges for blood levels of antidepressant medications are useful in optimizing medication dosing (201, 232, 233).

Individual differences are common in the time to response and the tolerability of treatments. For patients who have shown a partial response to treatment, particularly those with features of personality disorders and prominent psychosocial stressors, extending the antidepressant medication trial (e.g., by 4–8 weeks) may allow up to one-third of patients to respond more fully (417–419).

In patients who are receiving psychotherapy, similar principles apply in terms of monitoring and adjusting treatment in the context of nonresponse or difficulty tolerating psychotherapy (331). Factors to be considered include the frequency of sessions, the type of psychotherapy being used, the quality of the therapeutic alliance, and the possible need for medications in lieu of or in addition to psychotherapy. Whereas increasing the frequency of therapy sessions is a reasonable approach to nonresponse, this approach is based on clinical wisdom and has not been systematically studied.

b. Changing to other treatments

Changing to a different non-MAOI antidepressant medication is a common strategy for patients with treatment-resistant major depressive disorder, especially those who have not shown at least partial response to the initial medication regimen. Although there are no specific patient characteristics that predict which medication to choose (420), results from STAR*D suggest that changing to a second-step treatment results in additional remission rates of about 25%, and further changes are associated with continued remission, albeit at lower rates (about 13%–14%). Treatment can be changed to a non-MAOI antidepressant medication from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a TCA) (369, 421–422). Adding or changing to a depression-focused psychotherapy should also be considered for patients with major depressive disorder who do not respond fully to medication treatment. Other strategies for patients who do not respond adequately to pharmacotherapy include changing to an MAOI after allowing sufficient time between medications to avoid hazardous interactions (see Table 8). Transcranial magnetic stimulation could also be an option, as it appears to be safe and well tolerated (270, 280). In addition, it has shown small to moderate benefits in most (268, 270–272) but not all (269, 273) clinical trials and recent meta-analyses. Recent randomized trials suggest that quetiapine monotherapy also produces a greater reduction in depressive symptoms than placebo (423, 424), with comparable efficacy to duloxetine (424), although the potential side effects of second-generation antipsychotic treatment need to be taken into consideration. ECT remains the most effective therapy for patients with treatment-resistant symptoms (239, 425), although results of clinical trials differ on whether patients with medication-resistant symptoms have responses to ECT that are comparable to those of patients without documented medication resistance (426–428).

c. Augmenting and combining treatments

Pharmacotherapy can be combined with a depression-focused psychotherapy, both as an initial treatment plan, and as a strategy to address nonresponse to treatment in one modality or the other. See Section II.B.4.c above for further information about combining pharmacotherapy and psychotherapy.

Antidepressant medications can be augmented with another non-MAOI antidepressant or with other, nonantidepressant agents. The addition of a second non-MAOI antidepressant may be helpful, particularly for patients who have had a partial response to antidepressant monotherapy (429). One option is to add a second non-MAOI antidepressant medication from a different pharmacological class, taking care to avoid drug-drug interactions. Another option is to add an adjunctive, nonantidepressant medication—such as lithium, thyroid hormone, an anticonvulsant, a psychostimulant, or a second-generation (atypical) antipsychotic. More information about these strategies is given later in this section.

Some limited evidence and clinical experience support the addition of bupropion to an SSRI. This combination is generally well tolerated, although bupropion, a moderately potent inhibitor of CYP 2D6, increases blood levels of some SSRIs (430). In one study, combined treatment with bupropion and an SSRI resulted in better outcomes than either therapy alone (431). Another commonly used strategy is the combination of mirtazapine and an SSRI or

venlafaxine. Generally, mirtazapine 15–30 mg at bedtime is added to the incompletely effective antidepressant and titrated up to 45 mg/day on the basis of response and tolerability (432).

For patients with pronounced anxiety or persistent insomnia not adequately relieved by an SSRI or SNRI, adjunctive use of anxiolytic and sedative-hypnotic medications is common (433, 434). These include benzodiazepines such as clonazepam (435) and selective GABA agonists such as zolpidem (436) and eszopiclone (437). Buspirone has also been used adjunctively in anxious individuals (429). Although adjunctive therapy of anxiety or insomnia can hasten symptomatic relief, there is no evidence of sustained benefit, and some patients have difficulty stopping the anxiolytic or hypnotic medication (438, 439).

Lithium, thyroid hormone, and stimulants are sometimes combined with antidepressants to augment response. Lithium is the most extensively studied of these adjuncts (440–443) and may also reduce the long-term risk of suicide (444). The interval before full response to adjunctive lithium is said to be in the range of several days to 6 weeks. The blood level required to enhance the effects of antidepressants still has not been confirmed. If effective and well tolerated, lithium should be continued at least for the duration of acute treatment and perhaps beyond the acute phase for purposes of relapse prevention.

Thyroid hormone supplementation, even in euthyroid patients, may increase the effectiveness of antidepressant medication treatment, whether used as an augmentation agent (445, 446) or in combination with an antidepressant from the outset of therapy (447). The dose typically used for this purpose is 25 mcg/day of triiodothyronine, increased to 50 mcg/day if the response is inadequate after about a week. The duration of treatment required has not been well studied.

Second-generation antipsychotic medications may increase the rates of response or remission of depressive symptoms in patients who typically have not responded to more than two medication trials (448), even when psychotic symptoms are not present. Generally, in clinical practice, lower doses are used for antidepressant augmentation than for treatment of psychosis. For example, the combination of olanzapine and fluoxetine has been extensively studied (449–452) and is typically initiated with 6 mg of olanzapine and 25 mg of fluoxetine daily and titrated upward as tolerated to a maximum of 18 mg of olanzapine and 75 mg of fluoxetine daily. Aripiprazole has received FDA approval for augmentation of antidepressive agents and is typically initiated at 2.5–5 mg/day and titrated upward as tolerated to a maximum of 15 mg/day (453). With quetiapine, doses of 25 to 400 mg/day have been used, with benefits for depressive symptoms found in some (454, 455) but not all (456) clinical trials. Risperidone augmentation, in doses of up to 3 mg daily (457, 458) also appears to improve the response to antidepressant agents. In most of these trials, the onset of the effect of second-generation antipsychotic augmentation has been rapid, although the magnitude of the advantage relative to placebo has been relatively modest. In the only two trials to utilize active comparison groups, the combination of olanzapine and fluoxetine was not significantly more effective at study endpoint than continued therapy with nortriptyline (450) or venlafaxine (451). Naturalistic follow-up data also suggest that long-term weight gain can be problematic for many patients receiving second-generation antipsychotic augmentation therapy, particularly with the olanzapine-fluoxetine combination (459). In addition, a recent meta-analysis suggests that the rate at which SGA augmentation is discontinued is nearly four-fold greater than study discontinuation among subjects randomly assigned to placebo (448). When compared with other strategies for antidepressant nonresponders, augmentation with a second-generation antipsychotic carries disadvantages: the high cost of many agents, the significant risk of weight gain and other metabolic complications (e.g., dyslipidemia, hypertriglyceridemia, glucose dysregulation, diabetes mellitus), and potential risk of hyperprolactinemia, tardive dyskinesia, neuroleptic malignant syndrome, and QTc prolongation. Thus, the advantages and disadvantages of antipsychotic medications should be considered when choosing this augmentation strategy. In addition, when augmentation with a second-generation antipsychotic is effective, it is uncertain how long augmentation therapy should be maintained.

Many clinicians find that augmentation of antidepressants with low doses of stimulants such as methylphenidate or dextroamphetamine may help ameliorate otherwise suboptimally responsive depression (460–462), although not all clinical trials have shown benefits from this strategy (463). More recently, the novel compound modafinil has shown modest benefit when combined with SSRIs, related to specific effects on residual symptoms such as fatigue and hypersomnolence (464–467). Although there are no clear guidelines regarding the length of time stimulants or modafinil should be coadministered, in one extension study the effects of modafinil were maintained across 12 weeks of additional therapy (468). Physicians prescribing modafinil for this off-label use should become familiar with rare but dangerous cutaneous reactions to it, including reported instances of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (469), and cytochrome P450 interactions. Modafinil can also induce CYP 3A4 and render contraceptive medications and other medications metabolized through this route ineffective.

Although their use in this context has not been extensively evaluated, anticonvulsants such as carbamazepine, valproic acid, and lamotrigine may offer some benefit in the treatment of medication-resistant major depressive disorder (121, 429, 470–473).

A rarely used strategy is the combined use of a TCA or trazodone and an MAOI (474, 475). The combination of a TCA and an MAOI has been used for more than three decades for treatment of some of the most treatment-resistant depressive disorders; however, the risk of drug-drug interactions necessitates careful monitoring (119). Of particular concern with these combinations is the serotonin syndrome, characterized by delirium, hyperthermia, hyperreflexia, myoclonus, and, rarely, death (see Section II.B.2.b.5.b). Use of an MAOI in combination with a TCA and related antidepressants should probably not be considered until other pharmacological strategies for patients with treatment-resistant illness have been exhausted; psychiatrists and patients choosing to use the combination of an MAOI and a TCA should be well acquainted with the potential hazards and carefully weigh the relative risks and benefits of such a strategy.

Vagus nerve stimulation was approved for use in patients whose symptoms have not responded to at least four adequate trials of antidepressant medications and/or ECT. Acute benefits were not observed in the sham-controlled portion of the VNS trial (282). When compared with a parallel treatment-as-usual arm, the long-term (1–2 year) open-label extension showed small (476, 477) but persistent (478) improvements in symptoms with VNS that could be clinically significant for some patients. Other open-label studies have also shown some benefit when VNS is used simultaneously with pharmacotherapy (479–481).

As with any surgical device implantation, there is a small risk of postsurgical infection (482). A majority of individuals experience hoarseness or voice alteration during stimulation, and coughing, dyspnea, and neck discomfort are common (281, 481) but generally are tolerable to patients (282, 479). Patients also need to be informed of the implications of having an implanted VNS device for future medical care (482). For example, with a VNS device in place, brain MRI requires the use of a special send-receive coil. The VNS device may affect the operation of other implanted devices such as cardiac pacemakers or defibrillators and other procedures such as diathermy, and whole body or radiofrequency receive-only MRI are contraindicated. VNS is also contraindicated in the presence of bilateral or left cervical vagotomy.

Relative to other antidepressive treatments, the role of VNS remains a subject of debate. However, it could be considered as an option for patients with substantial symptoms that have not responded to repeated trials of antidepressant treatment.

C. CONTINUATION PHASE

Continuation phase pharmacotherapy is strongly recommended following successful acute phase antidepressant therapy, with a recommended duration of continuation therapy of approximately 4–9 months (assuming good and consistent control of depression symptoms). The goal of continuation treatment is to prevent relapse (i.e., the re-emergence of significant depressive symptoms or dysfunction) in the vulnerable period immediately following remission (i.e., a complete alleviation of symptoms) (408, 410, 411). The possibility of relapse should be carefully monitored during the continuation phase as this is when risk of relapse is highest (483). Within the first 6 months following recovery from a major depressive episode, relapse of depressive symptoms is common, with the proportion of patients with relapse ranging from 20% of patients in mixed samples (484–487) to as many as 85% of severely depressed inpatients receiving treatment with ECT (234, 488, 489). These studies also show that relapse rates are greater if antidepressant treatment (including ECT) is discontinued or reduced in dose or intensity following recovery (234, 489, 490). There is evidence that patients who do not completely recover during acute treatment have a significantly higher risk of relapse (and a greater need for continuation treatment) than those who have no residual symptoms (227, 491, 492). Similarly, patients who have not fully achieved remission with psychotherapy are at greater risk of relapse in the near term (364, 365, 367, 493, 494). To reduce the risk of relapse during the continuation phase, treatment should generally continue at the same dose, intensity, and frequency that were effective during the acute phase. Although the number of randomized controlled trials of antidepressant medications in the continuation phase is 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 4–9 months after achieving full remission (105, 225, 495).

Published studies for the continuation phase with older TCAs as well as newer medications have consistently shown efficacy of these medications in preventing relapse, compared with placebo. Lithium has also been shown to have efficacy in preventing relapse (496).

Cognitive-behavioral therapy may prevent relapse of depression when used as augmentation to medication treatment. It may also bestow an enduring, protective ben-

efit that reduces the risk of relapse after the treatment has ended (363). Cognitive group therapy helps to prevent relapse and recurrence for patients in remission after a major depressive episode (497). Mindfulness-based cognitive therapy is a variant of cognitive therapy that encourages patients to pay attention to their thoughts and feelings in the moment and to accept them rather than judging or trying to change or disprove them. Among patients with remitted depression, mindfulness-based cognitive therapy groups may reduce risk of relapse for patients who have already experienced three or more episodes (498). Such benefits for CBT (and potentially, for other psychotherapies) would offer an advantage over pharmacotherapy, which works only as long as the patient continues the antidepressant medication.

Continuation therapy is also essential in reducing relapse risk after an acute course of ECT (239). Although relapse occurs for many patients regardless of continuation strategy (234, 488, 489), remission of symptoms following successful treatment with ECT may be maintained with either pharmacotherapy or continuation ECT (234). Research shows that continuation ECT is comparable in efficacy to the combination of nortriptyline and lithium (234) and that the latter combination is superior to nortriptyline alone in preventing relapse (489). Although there is limited information regarding prognostic factors, relapse may be less likely among patients with melancholic depression who receive continuation ECT after remission with acute ECT than among those who receive continuation pharmacotherapy after remission with acute ECT (499).

Given the significant risk of relapse during the continuation phase of treatment, it is essential to assess depressive symptoms, functional status, and quality of life in a systematic fashion, which can be facilitated by the use of periodic, standardized measurements. It is often helpful for patients and families to identify particular signs (e.g., lack of engagement in specific activities that are usually enjoyed, specific "signal" symptoms or patterns of thought) that are typical of their earlier depressive episodes and may suggest the beginnings of a depressive relapse. Furthermore, any sign of symptom persistence, exacerbation, or reemergence or of increased psychosocial dysfunction during the continuation period should be viewed as a harbinger of possible relapse.

If a relapse does occur during the continuation phase, a return to the acute phase of treatment is required. An initial step is often to increase the dose of medication (500) or, with continuation ECT, to increase the frequency of treatment (501). For patients receiving psychotherapy, an increased frequency of sessions or a shift in the psychotherapeutic focus may be needed. It is also essential to determine whether any specific precipitants are contributing to the relapse of depression. For example, the onset or worsening of psychosocial stressors, substance use disorders, or general medical conditions can contribute to increased depressive symptoms. In addition, decreased treatment adherence or reductions in medication blood levels (e.g., due to drug-drug interactions or increased cigarette use) can also prompt a depressive relapse.

D. MAINTENANCE PHASE

Patients with chronic and/or recurrent major depressive disorder who complete the continuation phase without relapse proceed to the maintenance phase of treatment, in which the goal is to protect susceptible patients against recurrence of subsequent depression.

Patients who have had three or more prior major depressive episodes should receive maintenance treatment. Within the first 6 months following recovery from a major depressive episode, 20% of patients will experience a recurrence (484). Between 50% and 85% of patients will have at least one lifetime recurrence, usually within 2 or 3 years (502), although there is little consistency in the time to recurrence for any individual patient (484). Patients who have had a prior major depressive episode also have a high risk of experiencing subsequent affective episodes other than another major depressive episode, such as a manic, hypomanic, or dysthymic episode (503). The number of lifetime major depressive episodes is significantly associated with the probability of recurrence, such that the risk of recurrence increases by 16% with each successive episode (484).

Maintenance therapy should be considered more strongly for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, family history of mood disorders, and the severity of prior episodes (504) (see Table 10). Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the presence of side effects during continuation therapy, and the severity of prior depressive episodes, including factors such as psychosis or suicide risk. Due to the risk of recurrence and the importance of early detection of recurrent symptoms, patients should be monitored periodically and in a systematic fashion during the maintenance phase; such assessments can be facilitated by the use of standardized rating scales, as described in Section II.A.8.

In general, the treatment that was effective in the acute and continuation phases should be used in the maintenance phase.

Among the therapeutic options available for maintenance treatment, antidepressant medications have received

TABLE 10. Risk Factors for Recurrence of Major Depressive Disorder

Persistence of subthreshold depressive symptoms
Prior history of multiple episodes of major depressive disorder
Severity of initial and any subsequent episodes
Earlier age at onset
Presence of an additional nonaffective psychiatric diagnosis
Presence of a chronic general medical disorder
Family history of psychiatric illness, particularly mood disorder
Ongoing psychosocial stressors or impairment
Negative cognitive style
Persistent sleep disturbances

the most study. There have been more than 30 trials of pharmacotherapy in the maintenance phase, and results have generally demonstrated the effectiveness of antidepressant medication for relapse prevention (105, 226, 314, 505–507). Many of these trials used TCAs (314, 506), although results of trials involving newer antidepressant medications have been assessed in a recent meta-analysis (507). Lithium has also been used as maintenance treatment for major depressive disorder (441). Despite this, there is limited information on many of the clinical decisions involving medication use in the maintenance phase. Even though lower doses of medication are less likely to produce side effects, results from one study suggest that full doses are superior to lower doses in the maintenance phase (508). Particularly if medications are well-tolerated, it is generally advisable to prescribe the same antidepressant medication doses for maintenance therapy that were effective in prior phases of treatment. Even with adequate maintenance treatment, pharmacotherapy is not invariably successful in preventing relapse and return of symptoms, which still occur in as many as 25% of individuals (509, 510). It is unclear whether some relapses during maintenance therapy are loss of therapeutic efficacy, a phenomenon that has been referred to as tachyphylaxis, but many such relapses appear related to inadequate prophylactic effects of medication (511). When relapses occur, clinicians typically address them using the same approaches described to treat incomplete responses to treatment, such as increasing the dose of medication, changing to a different medication, or adding another medication or a depression-focused psychotherapy to augment therapeutic response (510, 512).

There have been fewer investigations of the effectiveness of psychotherapy in the maintenance phase. Nonetheless, several studies have shown that acute psychotherapies for major depressive disorder also have maintenance benefits. For example, even once-monthly maintenance IPT has been shown to forestall relapse in patients at high risk for relapse (289, 314, 315, 513). Most of these studies have used once-monthly maintenance IPT, but research has not demonstrated that frequency of sessions affects outcome (289). In one study, maintenance cognitive therapy delivered over 2 years was as effective as maintenance medication for recurrent major depressive disorder (514). Combining psychotherapy—such as CBT, cognitive therapy, or IPT—with pharmacotherapy in the maintenance phase has also been considered by investigators. Some results suggest that the combination of antidepressant medications plus psychotherapy may be more effective in preventing relapse than treatment with single modalities (314, 365, 506, 515, 516).

For patients receiving treatment with pharmacotherapy and/or psychotherapy, the frequency of visits during the maintenance phase should be set according to the clinical condition and the specific treatments being used. The frequency can range from as low as once every several months for stable patients who require only psychiatric management and medication monitoring to as high as once or twice per week for those receiving psychodynamic psychotherapy. For CBT and IPT, maintenance-phase treatments usually involve a decreased frequency of visits (e.g., once a month). The duration of the maintenance phase will vary depending on the frequency and severity of prior major depressive episodes, the tolerability of treatments, and patient preferences. For many patients, some form of maintenance treatment may be required indefinitely.

Electroconvulsive therapy has also been used in the maintenance phase, although evidence for its benefits comes largely from case reports (239). Patients who exhibit repeated episodes of moderate or severe major depressive disorder despite optimal pharmacological treatment or patients who are medically ineligible for such treatment may be maintained with periodic ECT. Although the optimal frequency and duration of maintenance phase ECT treatments has not been well studied, maintenance ECT is often administered monthly; individuals for whom this is insufficient may find treatment at more frequent intervals to be beneficial (501).

E. DISCONTINUATION OF TREATMENT

If maintenance-phase treatment is not indicated, stable patients may be considered for discontinuation of treatment after the continuation phase. The precise timing and method of discontinuing psychotherapy and pharma-

cotherapy for major depressive disorder have not been systematically studied.

The decision to discontinue treatment should be based on the same factors considered in the decision to initiate maintenance treatment (Table 10), including the probability of recurrence, the frequency and severity of past episodes, the persistence of depressive symptoms after recovery, the presence of co-occurring disorders, and patient preferences. The type of treatment being received may also play a role in the decision making. In general, psychotherapy has a longer lasting treatment effect and carries a lower risk of relapse following discontinuation than pharmacotherapy. In terms of timing, patients should be advised not to discontinue medications before holidays, significant events (e.g., weddings), or stressful events.

Patients should be carefully monitored during and immediately after treatment discontinuation to ensure that remission is stable. The highest risk for a relapse is seen in the first 2 months after discontinuation of treatment. Hence, it is important to schedule a follow-up visit during this period to ensure stability.

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. Such tapering allows for the detection of recurring symptoms at a time when patients are still partially treated and therefore more easily returned to full therapeutic treatment if needed. In addition, such tapering can help minimize the incidence of antidepressant medication discontinuation syndromes, particularly with paroxetine and venlafaxine (98, 163, 164). Discontinuation syndromes are problematic because their symptoms include disturbances of mood, energy, sleep, and appetite and can therefore be mistaken for or mask signs of relapse (517). Consequently, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. Discontinuation syndromes have been found to be more frequent after discontinuation of medications with shorter half-lives, and patients maintained on short-acting agents should have their medications tapered gradually over a longer period (518, 519). Another strategy is to change to a brief course of fluoxetine, e.g., 10 mg for 1–2 weeks, and then discontinue the fluoxetine (165). The psychiatrist should closely monitor patients withdrawing from antidepressants and provide reassurance that symptoms are time-limited and can be addressed by more gradual tapering (see Section II.B.2.b.1.i).

How to end psychotherapy is typically dependent on the type of therapy. For time-limited approaches, termination is usually broached from the initiation of treatment and periodically revisited, as the therapist-patient dyad notes which session they are in, how many remain, and how they have progressed toward defined goals. In dynamically oriented psychotherapy, the therapist typically raises termination as an issue well in advance of the final session, using the opportunity to explore remaining and unresolved issues in transference.

Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse. Early signs of major depressive disorder should be reviewed, often with a family member, and a plan established for seeking treatment in the event of recurrent symptoms. Patients should continue to be monitored over the next several months to identify early evidence of recurrent symptoms. Again, systematic assessment of symptoms, side effects, adherence, and functional status during this period of high vulnerability is strongly recommended. If a patient does suffer a recurrence after discontinuing medication, treatment should be promptly reinitiated. Usually, the previous treatment regimen to which the patient responded in the acute and continuation phases should be reinitiated (520). Patients who have a recurrence following discontinuation of antidepressant therapy should be considered to have experienced another major depressive disorder episode and should receive adequate acute-phase treatment followed by continuation-phase treatment and possibly maintenance-phase treatment.

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

A. PSYCHIATRIC FACTORS

1. Depressive symptoms

a. Suicidal ideation and behaviors

Because suicide is the worst outcome of major depressive disorder, a patient's risk for suicide must be assessed repeatedly over the course of treatment. For patients who report suicidal ideation, intention, or planning, close surveillance is necessary (see Sections II.A.3 and II.A.4). Psychiatrists should consider greater intensity of treatment for suicidal patients, including hospitalization when warranted and/or combined treatment with pharmacother-

apy and psychotherapy. In patients at high risk for suicide and in whom a particularly rapid antidepressant response is required, consideration should be given to the use of ECT (239, 243, 521). Patients with major depressive disorder who present to an emergency department with suicidal ideation, or who have made a suicide attempt, should be triaged to determine their level of safety and establish the appropriate level and setting of care. Upon entrance to the emergency department, they should be searched to permit removal of potentially dangerous items, such as weapons and personal belongings that could cause harm (e.g., sharp objects, belts, shoes, medications). Factors to consider in determining the nature and intensity of treatment include (but are not limited to) access to and lethality of suicide means, past and family history of suicidal behavior, co-occurring substance abuse, the availability and adequacy of social supports, and the nature of the doctor-patient alliance.

To lower the risk of suicide, the psychiatrist should also treat modifiable risk factors, such as anxiety (especially panic attacks), insomnia, agitation, psychotic symptoms, and substance abuse (22), in addition to treating the major depressive episode. Among inpatients who died by suicide, Busch et al. (522) observed that a great majority were admitted for indications other than suicidal ideation, and anxiety and agitation were common, suggesting that such symptoms should be addressed if they are present. Family members can also play an important role in detecting and preventing suicidal behaviors. When permitted by the patient, the psychiatrist should educate those close to the patient concerning appropriate interventions and encourage communication.

There has been a growing controversy about the risk of suicidal ideas and behaviors (sometimes referred to as "suicidality") after initiation of antidepressant treatment. Although information on such risk continues to evolve, a predictive relationship to suicide has never been demonstrated. Clinical experience has long suggested that patients may develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness if neurovegetative and psychomotor symptoms respond to antidepressant treatment before mood improves. More recently, meta-analyses of data from clinical trials have shown statistically significant increases in suicidal thoughts or behaviors in individuals age 25 years or younger who are treated with antidepressant medication, compared with placebo, with an approximately 1.5- to 2.5-fold increase in the relative risk (26, 523–530). In percentage terms, it is estimated that one to three of 100 individuals age 25 years or younger could potentially have an increase in suicidal thoughts or behaviors with antidepressant treatment (26), although there has been no evidence of increased mortality in the study subjects as a result of suicide (531). To alert clinicians to the need for vigilance and communication during the initial phase of antidepressant treatment, the FDA has issued a black-box warning pertaining to children, adolescents, and young adults that advises of this increase in the risk of suicidal thinking and behavior; information on the warning is available on the FDA Web site at http://www.fda.gov/cder/drug/antidepressants/default.htm. In making decisions about treatment, this awareness of a potential increase in suicidal thinking and behavior in children, adolescents, and young adults must be balanced against the negative effects, including suicide, of untreated depression (532) as well as the demonstrated benefits of antidepressant treatment (523, 533–535). For adults age 65 years or older, a review of the evidence from clinical trials showed a decrease in the risk of suicidal thinking or behaviors with antidepressant treatment, with no change in risk detected for other adults (age 25 to 64 years) (536).

For additional details about the treatment of suicidal individuals, clinicians are encouraged to consult APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (22).

b. Major depressive disorder–related cognitive dysfunction

Cognitive inefficiency and impairment are common features of major depressive disorder. Many depressed patients report slowed thoughts, poor concentration, distractibility, and reduced capacity to process information. They also display diminished attention to self-care and to their environment. Transient cognitive impairment, especially involving attention, concentration, and memory storage and retrieval, are demonstrable through neuropsychological testing (537). In extreme cases, especially in elderly patients, these deficits are so prominent that patients appear to have dementia. For individuals who exhibit symptoms of a dementia syndrome, it is crucial that any underlying depressive disorder be identified and treated.

Among depressed patients, the differential diagnosis of cognitive dysfunction includes degenerative dementias (such as Alzheimer's disease and Pick's disease) and reversible causes (such as vitamin B_{12} deficiency, folate deficiency, testosterone deficiency, substance use). Several clinical features help distinguish major depressive disorder–related cognitive dysfunction from other dementia syndromes. When performing cognitive tasks, depressed patients generally exert less effort and report greater incapacity than do patients with dementia. The latter, especially in more advanced stages, typically do not recognize their cognitive failures, since insight is impaired. In contrast, depressed patients may report being unable to think or remember. Patients with major depressive disorder–related cognitive

dysfunction lack the signs of cortical dysfunction (i.e., aphasia, apraxia, agnosia) encountered in dementias such as Alzheimer's disease (538, 539). Nevertheless, distinguishing dementia from depression-related cognitive dysfunction can be difficult, particularly as the two may coexist. For further discussion of the co-occurrence of dementia and depression, the reader may also wish to consult APA's *Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias, Second Edition* (539).

The detection of major depressive disorder–related cognitive dysfunction alerts the psychiatrist to the need for treatment of the underlying major depressive disorder, which should in turn reduce the signs and symptoms of the cognitive dysfunction. Although initially reversible, major depressive disorder–related cognitive dysfunction increasingly appears to be a harbinger of subsequent dementia (540, 541). In addition, research suggests that certain types of executive cognitive dysfunction predict greater disability and limited treatment response in geriatric patients with depression (542, 543).

2. DSM depressive subtypes

a. Psychotic features

Major depressive disorder is sometimes accompanied by hallucinations or delusions, which may be congruent or incongruent with the depressed mood. Recognition of psychosis is essential among patients with major depressive disorder as it is often undetected, resulting in ineffective treatment (544–546). Psychotic features constitute a risk factor for recurrent major depressive disorder and recurrent psychosis and hence indicate the need for maintenance treatment.

Electroconvulsive therapy is highly effective in treating psychotic depression (241) and can be considered as a first-line treatment option whenever major depressive disorder is associated with psychotic features (239, 243, 547). Pharmacotherapy can also be used as a first-line treatment option for major depressive disorder with psychotic features. Psychotic depression typically responds better to the combination of an antipsychotic and an antidepressant medication rather than treatment with either component alone (547–549), although some research has shown comparable responses for antidepressive treatment or antipsychotic treatment alone (550, 551). Lithium augmentation is helpful for some patients who have not responded to combined treatment with antidepressant and antipsychotic medication (262, 552).

b. Catatonic features

A catatonic syndrome sometimes occurs in the context of major depressive disorder (553–556) and is characterized by at least two of the following manifestations: immobility, as evidenced by catalepsy or stupor; extreme agitation; extreme negativism; peculiarities of voluntary movement, as evidenced by posturing, stereotyped movements, mannerisms, or grimacing; and echolalia or echopraxia (556, 557). The presence of catatonia should prompt a thorough differential diagnosis as it can also occur in association with general medical conditions and with several other psychiatric disorders, including bipolar disorder and schizophrenia (556, 558, 559). Catatonic signs often dominate the clinical presentation and may be so severe as to be life-threatening, compelling the consideration of urgent somatic treatment. Patients with catatonic features may also need supportive medical interventions including hydration, nutrition, prophylaxis against deep vein thrombosis, turning to prevent bed sores, and passive range of motion to prevent contractures. Intravenous administration of a benzodiazepine (e.g., lorazepam, diazepam) or a barbiturate (e.g., amobarbital) may induce rapid relief (242, 553) and can be followed by continued oral administration for patients who show an initial response. When such intervention is ineffective, the clinician should consider the urgent use of ECT (239, 242). The efficacy of ECT in catatonia is well documented in the case series literature (239) and is usually apparent after a few treatments. After catatonic manifestations recede, antidepressant medication treatments may be needed during acute and maintenance phases of treatment. In addition to antidepressant medications, ongoing treatment may include ECT, lithium, antipsychotics, or a combination of these approaches, depending upon the patient's condition. Patients with catatonia may have an increased susceptibility to neuroleptic malignant syndrome when exposed to antipsychotic medications (560), and this should be considered in planning treatment.

c. Melancholic features

Melancholic features describe characteristic somatic symptoms, such as the loss of interest or pleasure in all, or almost all, activities or a lack of reactivity to usually pleasurable stimuli. Other symptoms include worsened depression in the morning, early morning awakening, and significant anorexia or weight loss, among others (16). Major depressive disorder with melancholic features is responsive to both pharmacotherapy and ECT. Serotonin norepinephrine reuptake inhibitors and TCAs may have an advantage over SSRIs for this patient population (561, 562). Psychotherapy may be less appropriate for patients with melancholia (563), particularly if the symptoms prevent engagement with the therapist (e.g., lack of interest in activities). Major depressive disorder with melancholic features may also be associated with an added risk of sui-

cide (564) and an increased risk of subsequent recurrence despite the use of maintenance pharmacotherapy (509).

d. Atypical features

Major depressive disorder with atypical features is characterized by a pattern of marked mood reactivity and at least two additional symptoms, including leaden paralysis, a long-standing pattern of interpersonal rejection sensitivity, significant weight gain or increase in appetite, and hypersomnia (the latter two of which are considered reversed vegetative symptoms) (16). The phrase "atypical features" distinguishes this depressive subtype from the more classical "endogenous" presentation of depression, but it does not connote an uncommon or unusual form of depression. Atypical features are more common in women, are associated with an earlier age at onset of depression and a greater degree of associated anxiety disorders, and frequently have a more chronic, less episodic course, with only partial interepisode recovery (565, 566). These atypical features are also common in the depressed phase of bipolar I disorder and bipolar II disorder (567, 568), indicating a need for careful screening for manic or hypomanic episodes in patients who present with atypical depressive symptoms.

In the treatment of major depressive disorder with atypical features, MAOIs have greater efficacy than TCAs (122, 569–572). Some data also support the use of SSRIs, bupropion, and CBT in this patient population (573–577). Electroconvulsive therapy is also effective in treating patients with atypical features (578). The presence and severity of specific symptoms as well as safety considerations should help guide the choice of treatment for major depressive disorder with atypical features. For example, if a patient does not wish to, cannot, or appears unlikely to adhere to the dietary and medication precautions associated with MAOI treatment, the clinician should consider alternative antidepressant medication or psychotherapy.

e. Seasonal pattern

A seasonal pattern of major depressive disorder is characterized by a regular temporal relationship between particular periods of the year and the onset and remission of symptoms, which is not the result of seasonally related psychosocial stressors (e.g., seasonal unemployment, significant anniversaries). The most common presentation in the northern hemisphere is the regular appearance of symptoms between early October and late November and regular remission from mid-February to mid-April. Episodes of major depressive disorder with seasonal pattern frequently have atypical features such as hypersomnia and overeating. Some of these patients experience manic or hypomanic episodes as well; hence, it is important to diagnose bipolar disorder when appropriate.

The entire range of treatments for major depressive disorder may be used to treat major depressive disorder with seasonal pattern, either in combination with or as an alternative to light therapy. As a primary treatment, light therapy may be recommended as a 1- to 2-week time-limited trial (395), primarily for outpatients with clear seasonal patterns. For patients with more severe forms of major depressive disorder with seasonal pattern, the use of light therapy is considered adjunctive to pharmacological intervention. In terms of specific antidepressive agents, the extended release formulation of bupropion is FDA approved for use with patients who have major depressive disorder with seasonal pattern.

3. Co-occurring psychiatric disorders

Co-occurring psychiatric disorders generally complicate treatment. Patients with major depressive disorder who also have other psychiatric disorders have greater symptom severity and are more challenging to treat than patients with major depressive disorder alone. Yet the presence of co-occurring Axis I or Axis II disorders should not lead clinicians to conclude that patients are untreatable. Furthermore, other Axis I or Axis II disorders may masquerade as major depressive disorder or may seem to co-occur with the depression. In these cases, the other apparent disorders evanesce with successful treatment of the underlying major depressive disorder.

a. Dysthymic disorder

Dysthymic disorder is a chronic mood disorder with symptoms that fall below the threshold for major depressive disorder. Because of this, it may escape notice and may be inadequately treated. Nonetheless, it can cause significant suffering and disability. In some patients, both dysthymic disorder and major depressive disorder (so-called "double depression") may be diagnosed.

In the treatment of dysthymic disorder and chronic major depressive disorder, there is demonstrated efficacy for antidepressant medications, including TCAs, SSRIs, other newer agents, and MAOIs. Unfortunately, clinical trials provide little evidence of the relative efficacies of particular agents (105, 579). In general, pharmacotherapy of dysthymic disorder resembles that for episodes of major depressive disorder; responses to antidepressant medications by patients with dysthymic and chronic major depressive disorders have been comparable to the responses by patients with major depressive disorder episodes (580). In "double depression," antidepressant medication can reverse not only the acute major depressive episode but also the co-occurring dysthymic disorder (581).

Patients with dysthymic disorder, as well as patients with chronic and severe major depressive disorder, typically have a better response to the combination of pharmacotherapy and psychotherapy than to either alone (294, 295), although results of combined treatment studies have been mixed and complicated by methodological problems (582).

b. Anxiety disorders

As a group, anxiety disorders are the most commonly occurring psychiatric disorders in patients with major depressive disorder (583). A 2005 epidemiological study found that among individuals with major depressive disorder, 62% also met the criteria for generalized anxiety disorder, 52% for social phobia, 50% for posttraumatic stress disorder (PTSD), 48% for panic disorder, 43% for specific phobia, and 42% for obsessive-compulsive disorder (584). In addition, agitation and anxiety, including panic attacks, are frequent co-occurring symptoms of major depressive disorder. The appearance of anxiety and agitation in patients in a major depressive episode, particularly when accompanied by racing or ruminative thoughts, should alert the clinician to the possibility of a mixed mood state of a bipolar spectrum disorder (585).

In studies of major depressive disorder with a co-occurring anxiety disorder, both depressive symptoms and anxiety symptoms respond to antidepressant medication treatment (586). However, TCAs and SSRIs may initially worsen rather than alleviate anxiety symptoms, including panic attacks; patients should be so advised, and these medications should be introduced at low doses and slowly increased when treating such patients. Adjunctive antipanic agents, such as benzodiazepines, may be necessary as well. Selective serotonin reuptake inhibitors are beneficial for patients with co-occurring depression and social anxiety disorder (587) and co-occurring depression and PTSD (588). Bupropion is comparable to SSRIs in the treatment of patients with major depressive disorder and low to moderate levels of anxiety (82), but studies vary as to whether bupropion is (589) or is not (590) effective in the treatment of panic disorder. Because benzodiazepines are not antidepressants and carry their own adverse effects and toxicity, including abuse and dependence, benzodiazepines should not be the primary pharmacological agents for patients with major depressive disorder who have co-occurring anxiety symptoms. These agents may be used adjunctively with other antidepressive treatments, however (591). Psychotherapies such as CBT, behavioral therapy, and IPT may also be used to treat anxiety symptoms in the context of major depressive disorder (591, 592).

Obsessive-compulsive symptoms are also common in patients with major depressive episodes. In addition, obsessive-compulsive disorder may appear as a co-occurring condition in some patients with major depressive disorder. Clomipramine and SSRIs have demonstrated efficacy in managing obsessive-compulsive symptoms in addition to treating depression (593–595).

c. Dementia

Patients with dementia are predisposed to depression, and the psychiatrist should therefore screen for depression in this population, although this is sometimes challenging (539). One screening tool is the Cornell Scale for Depression in Dementia, which incorporates self-report with caregiver and clinician ratings of depressive symptoms (596). Treatment of major depressive disorder in the cognitively impaired patient requires careful supervision and monitoring of the patient's pharmacotherapy; this may entail education of home health aides, nursing home staff, and others. Antidepressants are likely to be efficacious in treatment of depressive symptoms, but they do not improve cognition, and data on antidepressant use in patients with dementia are limited (597–599). Individuals with dementia are particularly susceptible to the adverse effects of muscarinic blockade on memory and attention. Therefore, individuals with dementia generally do best when given antidepressant medications with the lowest possible degree of anticholinergic effect, e.g., bupropion, fluoxetine, sertraline, trazodone, and, of the tricyclic agents, desipramine or nortriptyline (600). Alternatively, some patients do well when given stimulants in small doses. Electroconvulsive therapy is also effective in major depressive disorder superimposed on dementia. It should be used if medications are associated with an excessive risk of adverse effects, are not tolerated, or if immediate resolution of the major depressive disorder episode is medically indicated (such as when it interferes with the patient's acceptance of food). In individuals with dementia, ECT treatment may be associated with a transient worsening of the patient's cognitive status (239, 601, 602). APA's *Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias, Second Edition* (539) contains more information about the treatment of depression and dementia.

d. Substance use disorders

Major depressive disorder frequently occurs with alcohol or other substance abuse or dependence. Therefore, the psychiatrist should obtain a detailed history of the patient's substance use. With the patient's permission, family members, friends, or co-workers can be collateral sources of information. If the evaluation reveals a substance use disorder, this should be addressed in treatment. A patient with major depressive disorder who has a co-occurring

substance use disorder is more likely to require hospitalization, more likely to attempt suicide, and less likely to adhere to treatment than a patient with major depressive disorder of similar severity uncomplicated by substance use (603–608).

Detoxifying patients before initiating antidepressant medication therapy is advisable when possible (110). Antidepressants may be used to treat depressive symptoms following initiation of abstinence if symptoms do not improve over time. It is difficult to identify patients who should begin a regimen of antidepressant medication therapy soon after initiation of abstinence, because depressive symptoms may have been induced by intoxication and/or withdrawal of the substance. A family history of major depressive disorder, a history of major depressive disorder preceding alcohol or other substance abuse, or a history of major depressive disorder during periods of sobriety raises the likelihood that the patient might benefit from antidepressant medication, which may then be started early in treatment. Comparing the temporal pattern of symptoms with the periods of use and abstinence of the substance may help to clarify the patient's diagnosis. Repeated, longitudinal psychiatric assessments may be necessary to distinguish substance-induced depressive disorder from co-occurring major depressive disorder, particularly because some individuals with substance use disorders reduce their substance consumption once they achieve remission of a co-occurring major depressive disorder.

Co-occurring substance use, especially with stimulant drugs, raises the risk of deleterious interactions with MAOIs, although few such events have been reported (609). Benzodiazepines and other sedative-hypnotics carry the potential for abuse or dependence and should rarely be prescribed to patients with co-occurring substance use disorders, except as part of a brief detoxification regimen. Hepatic dysfunction and hepatic enzyme induction frequently complicate pharmacotherapy of patients with alcoholism and other substance abuse. These conditions may require careful monitoring of blood levels (as appropriate for the medication), therapeutic effects, and side effects to avoid the opposing risks of either psychotropic medication intoxication or underdosing.

For individuals with nicotine dependence who wish to stop smoking, bupropion and nortriptyline treatment increase smoking cessation rates by about twofold (109) and would be useful to consider when selecting a specific antidepressive agent (110).

e. Personality disorders

For patients who exhibit symptoms of both major depressive disorder and a personality disorder, psychiatrists should consider appropriate treatment for each. Major depressive disorder should generally be the initial target; if evidence of a personality disorder persists when the depressive symptoms have resolved, psychotherapeutic and adjunctive pharmacotherapeutic approaches may be helpful (610–615). Patients with virtually any personality disorder exhibit a less satisfactory antidepressant medication treatment response, in terms of both social functioning and residual major depressive disorder symptoms, than do individuals without personality disorders (616). Personality disorders tend to interfere with treatment adherence and development of a psychotherapeutic relationship. Furthermore, many personality disorders increase the risk of episodes and increase time to remission of major depressive disorder (617, 618). Patients with various personality disorders also showed high rates of new-onset major depressive episodes in a large prospective study (619) and were at higher risk of attempting suicide than patients without a co-occurring personality disorder (620).

Axis II diagnoses should be made with caution during a major depressive episode, as depressive symptoms may exaggerate or mimic personality traits. Treatment of the depressive disorder for these patients can cause the apparent personality disorder symptoms to remit or greatly diminish. Depressed patients may believe that their current symptoms have been present from early life, when in fact they only began with the current episode. Such misperceptions often hinder accurate diagnosis. Some Cluster C personality disorders (e.g., avoidant, dependent, obsessive-compulsive) may reflect the residual impact of recurrent depressive symptoms and may remit with maintenance therapy (621).

Patients with borderline personality disorder have a particularly high rate of major depressive disorder: 20% in a community sample (622) and 50% in clinical samples (623). About 10%–15% of patients with major depressive disorder have co-occurring borderline personality disorder (624), and the percentage increases significantly in hospital and partial hospital samples. Patients with borderline personality disorder often exhibit mood lability, rejection sensitivity, inappropriate intense anger, and depressive "mood crashes." These symptoms are also common in patients with depression, particularly with atypical features, complicating the diagnosis of these disorders. Antidepressants are in general less effective in treating depressive episodes in patients with major depressive disorder and borderline personality disorder (625–629), with an overall response rate to all therapies of 20% (630).

For patients with major depressive disorder and borderline personality disorder, the personality disorder must also be addressed in treatment. Symptoms of both disorders can initially be treated with an SSRI or SNRI. Behavioral impulsivity and dyscontrol can also be treated

with low-dose antipsychotics, lithium, and some antiepileptic medications. Monoamine oxidase inhibitors, although efficacious, are not recommended due to the risk of serious side effects and the difficulties with adherence to dietary restrictions. Psychotherapeutic approaches such as dialectical behavioral therapy and psychodynamic psychotherapy have been useful in treatment of borderline personality disorder as well. In patients with borderline personality disorder particular attention must be paid to the maintenance of therapeutic rapport, which is frequently disrupted, and to the risk of self-harm and suicide, which occurs in 8%–10% of such individuals. More information about the treatment of borderline personality disorder can be found in APA's *Practice Guideline for Treatment of Patients With Borderline Personality Disorder* (610).

f. Eating disorders

Eating disorders are also common in patients with major depressive disorder (631). Selective serotonin reuptake inhibitors are the best studied medications for treatment of eating disorders, with fluoxetine having the most evidence for the effective treatment of bulimia nervosa (170). Antidepressants may be less effective in patients who are severely underweight or malnourished, and normalizing weight should take priority in these patients. Although SSRIs and psychotherapy are widely used for patients with anorexia nervosa, the evidence base on which these practices rest is modest. Patients with chronic anorexia nervosa have in general been less responsive to formal psychotherapy. On the other hand, evidence strongly supports the use of CBT in the treatment of bulimia nervosa. Other therapies (e.g., IPT, group therapies, family therapy) and medications such as SSRIs have also been studied and have demonstrated effectiveness for this disorder. Bupropion should be avoided in individuals with eating disorders due to the increased risk of seizures in these patients. Electroconvulsive therapy has not generally been useful in treating eating disorder symptoms. Although there are few data to guide treatment of co-occurring major depressive disorder and eating disorders, it is reasonable to optimize treatment of both disorders based on these and other considerations. More information about the treatment of eating disorders can be found in APA's *Practice Guideline for the Treatment of Patients With Eating Disorders, Third Edition* (170).

B. DEMOGRAPHIC AND PSYCHOSOCIAL VARIABLES

1. Major psychosocial stressors

Major depressive disorder may follow a substantial adverse life event, especially one that involves the loss of an important relationship or life role. This is particularly true in initial episodes of depression, with psychosocial stressors being less associated with the onset of recurrent episodes (632). Lower socioeconomic status, nonmarried status, unemployment, urbanization, and violent trauma seem to increase the risk of developing major depressive disorder, whereas religious belief may decrease it (633–635). Among those exposed to trauma, the prevalence of major depressive disorder seems to be higher among persons who develop PTSD than among those who do not (636). A recent meta-analysis underlined that among refugees, PTSD was diagnosed in one of 10 and one in 20 had major depressive disorder (637).

Marital discord has been identified as a potent risk factor in women for the development of depression (638, 639). Problems in the family setting may become an ongoing stressor that hampers the patient's response to treatment. Ambivalent, abusive, rejecting, or highly dependent family relationships may predispose an individual to major depressive disorder. The psychiatrist should screen for such factors and consider family therapy, as indicated, for these patients. Family therapy may be conducted in conjunction with individual and pharmacological therapies. Even for instances in which there is no apparent family dysfunction, it is important to provide the family with education about the nature of the illness and to enlist the family's support and cooperation with the treatment.

The psychiatrist may choose to treat a major depressive episode with an antidepressant, even if a major stressor preceded the episode. Nonetheless, attention to the relationship of both prior and concurrent life events to the onset, exacerbation, or maintenance of major depressive disorder symptoms is an important aspect of the overall treatment approach and may enhance the therapeutic alliance, help to prevent relapse, and guide the current treatment. A close relationship between a life stressor and major depressive disorder suggests the potential utility of a psychotherapeutic intervention coupled, as indicated, with somatic treatment.

2. Bereavement

Bereavement is a particularly severe stressor that can trigger a major depressive episode. However, grief, the natural response to bereavement, resembles depression, and this sometimes causes confusion. Psychiatrists treating bereaved individuals should differentiate symptoms of normal acute grief, complicated grief, and major depressive disorder, as each of these disorders requires a unique management plan. Normal grief should be treated with support and psychoeducation about symptoms and the course of mourning; complicated grief requires a targeted psychotherapy, with or without concomitant medication (535,

640); and major depressive disorder should be treated with medication and/or depression-focused psychotherapy.

Acute grief is the universal reaction to loss of a loved one, and it is a highly dysphoric and disruptive state (641). Acute grief is characterized by prominent yearning and longing for the person who died, recurrent pangs of sadness and other painful emotions, preoccupation with thoughts and memories of the person who died, and relative lack of interest in other activities and people. Despite the similarity with depression, only about 20% of bereaved people meet the criteria for major depressive disorder. Successful mourning leads to resolution of acute grief over a period of about 6 months. Integrated grief remains as a permanent state in which there is ongoing sadness about the loss often accompanied by ongoing feelings of yearning for the person who died. However, when the death is accepted, and grief integrated, the person is again interested in his or her own life and other people.

Complicated grief is a recently recognized syndrome in which symptoms of acute grief are prolonged, associated with intense and persistent yearning and longing for the deceased person, and complicated by guilty or angry ruminations related to the death and/or avoidance behavior. Studies of individuals bereaved by the attacks of September, 11, 2001, have demonstrated that complicated grief is a distinct condition from either major depressive disorder or PTSD (642, 643). It is important to note that treatment for depression is not effective in relieving symptoms of complicated grief (640).

Although DSM-IV-TR excludes the diagnosis of major depressive disorder during the first 2 months following bereavement, major depressive disorder in the wake of bereavement can impede the course of mourning. Bereavement-related depression responds to antidepressant medication and should be treated; otherwise it is likely to become chronic and impairing (644). There is no indication that depression in the context of bereavement differs from other major depressive episodes, and data indicate that chronicity of bereavement-related depression over 13 months is similar to chronicity of depression in other contexts (644).

3. Culture and ethnicity

An appreciation of cultural and ethnic variables is important to the accurate diagnosis of major depressive disorder and in the selection and conduct of psychotherapy and pharmacotherapy (645–647). Although major depressive disorder is seen across cultural and ethnic groups, and the age at onset, gender differences, and prevalence of co-occurring conditions are similar across cultures, the actual incidence and prevalence of depression vary (648–656). Furthermore, some evidence suggests that patients of different cultures express depressive symptoms differently, particularly somatic and psychomotor symptoms (657). Specific cultural variables may also influence the assessment of major depressive disorder symptoms. For example, in some cultures, depressive symptoms may be more likely to be attributed to physical diseases (658). In addition, language barriers can impede accurate psychiatric diagnosis and effective treatment (659), and, even when speaking the same language, individuals of different cultures may use different psychological terms to describe their symptoms (6, 7). In addition, the importance of individual experience should not be underestimated in the therapeutic relationship (660). The assessment and treatment process can also be influenced by religious beliefs (5). Individuals with high levels of religious involvement may have diminished rates of major depressive disorder (661, 662).

Differences in the utilization of psychiatric services by some cultural and ethnic groups have been well documented. Relative to Caucasians, African Americans and Latinos appear less likely to receive treatment for mood disorders (663–665).

Several studies have underscored the lower frequency of use of antidepressant drugs (and more specifically, SSRIs) (648, 666–669), ECT (670), and psychotherapy (671, 672) in minority groups, compared with Caucasians. If treatment for depression is initiated, African Americans are disproportionately more likely to receive pharmacotherapy (672), to drop out of treatment (673), and to develop chronic symptoms (674) than are Caucasian patients. These differences in mental health service use by minority populations appear to have a number of potential causes. Cultures and ethnicities may differ in the degree to which psychiatric illness is stigmatized (675) and in the preferences of individuals for treatment (676–678). For example, studies have found that Hispanic individuals were more likely to prefer counseling than whites, whereas African Americans varied across studies in their relative preference for counseling rather than pharmacotherapy (6, 679). Service use by minority populations is more affected by financial constraints (including those related to insurance) and social barriers (e.g., stigma) than the use of comparable services by Caucasians (664, 680, 681). In addition, pharmacological factors may play a role in patient preferences and adherence, as ethnic groups may differ in their relative rates of metabolism (682–684) and side effects and response to antidepressant medications (685–688).

4. Older age

The combined prevalence of major depression, dysthymic disorder, and "minor" depression in individuals over age

60 years has been reported to be as high as 25%, and major depressive disorder has been reported to be present in 14%–42% of nursing home residents (689). Elderly patients typically display more vegetative signs and cognitive disturbance but report less subjective dysphoria than younger patients. Major depressive disorder may consequently be misattributed to physical illness, dementia, or the aging process itself. For older adults with chronic illness or physical disability, including those expected to remain in a long-term care facility, depression may be erroneously regarded as expected or inevitable, and therefore untreatable (690). As a result, it is common for major depressive disorder to be undiagnosed and untreated among older adults.

As in all depressed individuals, a suicide risk assessment is an essential element of the evaluation process in older individuals. Although older adults constitute only 13% of the U.S. population, they account for 19% of all suicides, with elderly white men having the highest rates of completed suicides (691). This increase in suicide risk with aging in some demographic groups should be taken into consideration when estimating suicide risk and developing a plan to reduce such risk.

Several general medical conditions common among older adults are risk factors for depression. In addition, the presence of depression often exacerbates the course of the co-occurring medical condition and is a risk factor for poor outcomes. For example, elderly patients who are depressed and recovering from hip fractures have poorer functional outcomes from rehabilitative care and are less likely to return to full ambulation, compared with older adults with hip fractures who are not depressed (692–694). There is also frequent co-occurrence of major depressive disorder and cardiovascular disease; 25% or more of those with cardiovascular disease also have major depressive disorder, and co-occurring depression increases the morbidity and mortality of cardiovascular illness (695–697). The term vascular depression has been used to describe depression occurring in late life in patients with clinical evidence of cerebrovascular disease (698), although at this time it has not been established as a unique subtype of depression. In addition, major depressive disorder is a complication of cerebral infarction (see Section III.C.3). There is also a high prevalence of major depressive disorder among patients with dementia, and mood symptoms may precede cognitive symptoms and diagnosis of dementia (see Section III.A.3.C).

Just as patients with medical conditions should be screened for depression, patients exhibiting symptoms of depression should be thoroughly evaluated for the presence of co-occurring medical conditions, as major depressive disorder and general medical illnesses frequently coexist, especially in elderly patients (696, 699). This evaluation should include a systematic review of the patient's medications. Some medications have been reported to induce depressive symptoms (e.g., beta-blockers), although they may simply be producing lethargy and fatigue that mimic depression (700, 701). Consequently, the psychiatrist must carefully assess whether a given medication is contributing to depressive symptoms before prematurely altering what may be a valuable treatment. Patients undergoing their first major depressive episode in old age should be assessed for an undiagnosed neurological or other general medical disorder that may be responsible for the depressive symptoms. Similarly, frequently co-occurring symptoms of major depressive disorder, such as lassitude or pain, may mimic symptoms of a general medical condition. Pain in older adults, especially from orthopedic sources, may contribute significantly to the presence of depression in this population (702).

Once the patient has been thoroughly assessed, the treatment considerations for depressed geriatric patients are essentially the same as for younger patients. A meta-analysis has shown that SSRIs; TCAs; and cognitive-behavioral, behavioral, and psychodynamic therapies are all superior to placebo in the acute treatment for depression in subjects older than age 55 years (703–708). In addition, treatments for depression have been shown to be effective in nursing home populations (709, 710), as well as in inpatient and traditional outpatient settings of care. However, compared with younger individuals, older patients may be more likely to experience relapses and less likely to achieve a full response to treatment with antidepressant medications (711–714). In contrast, ECT is not only effective as a treatment for depression among older individuals, but those over age 65 years actually have better response rates than younger patients (715). Consideration should also be given to combined treatment with pharmacotherapy and psychotherapy, as evidence for the efficacy of stand-alone psychotherapy, such as CBT, is weak (716). Although the role of stimulants for antidepressant monotherapy is very limited, these compounds have some role in apathetic major depressive disorder in elderly patients with complicating general medical conditions. Late-life depression associated with vascular disease has also been found to respond well to treatment with antidepressants (717) and, in one unreplicated study, to TMS (718). Furthermore, in a recent randomized controlled trial, administering escitalopram prophylactically to patients who had experienced a stroke resulted in lower rates of depression at 12 months (334). Psychosocial factors are also frequent contributors to depression among older adults and should be addressed as part of the treatment plan (719, 720).

There are several considerations in prescribing medications for elderly patients. As with any patient, the psychiatrist should attempt to use as few medications as possible, and this is especially important given the complexity and multiplicity of issues in elderly patients. It is often useful to use medications that address several issues at once, such as choosing mirtazapine for a depressed, elderly patient with weight loss and insomnia. Elderly patients typically require a lower oral dose than younger patients to yield a particular blood level, and they tolerate a given blood level less well. Nevertheless, the blood levels at which antidepressant medications are maximally effective for elderly patients appear to be the same as those for younger patients (721, 722). Dose regimens should be adjusted for age-related metabolic changes, with close attention paid to hepatic and renal metabolic function. For patients who are receiving other medications, careful attention should be paid to potential drug interactions (160, 161, 723–725) (Tables 4 and 5).

Elderly patients are particularly prone to orthostatic hypotension and cholinergic blockade; for this reason, SSRIs, SNRIs, and other antidepressants should be considered over MAOIs or TCAs. Among the TCAs, desipramine and nortriptyline should be considered over amitriptyline, imipramine, and doxepin, due to increasing sensitivity to side effects and toxicity with advancing age. Treatment with SSRIs causes the syndrome of inappropriate antidiuretic hormone secretion (SIADH) at a higher rate in elderly patients than in younger patients (726, 727). Patients taking SSRIs have a three times greater risk of developing SIADH than patients taking other antidepressants, with the greatest risk among elderly patients (728).

For maintenance treatment, one study has shown that antidepressant medication (nortriptyline) and IPT are effective for elderly patients with recurrent major depressive disorder (315), yet a trend toward superior response was observed for combined pharmacotherapy and IPT, compared with pharmacotherapy alone. Another study demonstrated that paroxetine (but not monthly psychotherapy) was effective as maintenance therapy for elderly patients (729). For older patients with particularly severe or treatment-resistant depressive illness, addition of maintenance ECT to nortriptyline appears to improve treatment outcome (730). Among elderly patients who have had prior depression, the risk of developing another episode of major depressive disorder is substantially increased in those who develop or report sleep disturbance (731). Sleep disturbances may function as independent predictors of depression and are not simply prodromal depressive symptoms.

A body of systematic evidence suggests a particular value for various forms of collaborative or team-based care for elderly patients. Such care combines, for example, specialty mental health consultation/intervention with primary care management or community-based outreach and monitoring of care (732, 733). Older adults with depression can benefit from integration of mental health services in the setting where they typically receive their general medical care. It has been shown that support for algorithm-driven depression care processes within the primary care outpatient practice can lead to increased treatment adherence and improved clinical outcomes, including a reduction in mortality (734).

5. Gender

As part of the diagnostic assessment of a woman with major depressive disorder, there should be a detailed inquiry regarding reproductive life history and mood symptoms associated with reproductive life events, such as menses, use of oral contraceptive agents, peripartum, infertility, menopause, and pregnancy loss due to abortions, miscarriages, and perinatal losses. Although associations between reproductive factors and major depressive disorder are neither widespread nor consistent, some women may be particularly vulnerable to fluctuations in gonadal hormone levels (735). The perimenopausal transition has been identified as a high-risk period for new-onset major depressive disorder, with high variability of sex hormones as a risk factor (736, 737). Women in the perimenopausal transition may benefit from the use of serotonergic antidepressants, for mood and also for somatic symptoms such as hot flashes (738).

Since women are often caretakers in families, psychosocial stresses such as caring for an ill husband, child, or parent must be carefully assessed. Treating depressed mothers is associated with improved prognosis for their children as well (739). Maternal remission from depression was associated after 3 months with significantly decreased diagnoses and symptoms in their children, compared with children of mothers whose depression had not remitted. Thus, treating depressed mothers may crucially benefit both the patients and their children.

The patient's gender also factors into other treatment considerations for major depressive disorder. For example, the risks of certain adverse effects from treatments may also differ by gender. When prescribing trazodone to men, it is important to provide education about the risk of priapism (174). Older men typically have prostatic hypertrophy, making them particularly sensitive to anticholinergic effects of some antidepressants on the bladder outlet. While both men and women may experience de-

creased libido or anorgasmia while taking SSRIs, men may also experience ejaculatory dysfunction (740). Some women who are taking birth control pills require higher doses of TCA medications because of the induction of the hepatic enzymes responsible for medication metabolism. Similarly, medications that induce hepatic enzymes, such as anticonvulsants used as adjunctive treatment, reduce the effectiveness of contraceptives.

6. Pregnancy and postpartum

Major depressive disorder during pregnancy and postpartum presents unique treatment considerations. During these periods, approximately 10% to 15% of perinatal women will experience major depressive disorder, which is at least as common as rates reported for women in nonreproductive states (741, 742). Evaluation and communication of risks and benefits of antidepressants during pregnancy and breast-feeding is challenging and must include the risks of untreated maternal mood disorder, the limited body of research that informs safety of antidepressants, and the general lack of prospective long-term data following antidepressant exposure in utero and through lactation.

Depression-focused psychotherapy or other nonmedication therapies may be considered first for some women, and psychotherapy should be considered as part of the treatment plan whenever possible. As childbearing is a life stressor with psychosocial repercussions that may be amenable to psychotherapy, psychotherapy may serve to minimize medication exposure in some women. Although there is little controlled research, psychotherapies appear efficacious in antenatal and postpartum depression, with IPT being the best studied (743, 744). Therefore, depression-focused psychotherapies such as IPT and CBT should be considered in the treatment plan as a first-line treatment or in combination with medication to minimize medication exposure, especially if the individual has experienced a good response to a particular psychotherapy in the past or strongly prefers to avoid medication.

a. Depression during pregnancy

Psychiatrists should be familiar with the management of major depressive disorder in the context of pregnancy (745). More than 80% of women in the United States will have children (746), and about half of pregnancies are unplanned (747). Therefore, pregnancies—including unplanned pregnancies—are likely to occur during the course of treatment of major depressive disorder, as it is often a chronic and/or recurrent condition that is a major cause of disability during the reproductive years and disproportionately affects women, compared with men. In consideration of the high prevalence of both unplanned pregnancy and major depressive disorder in women, the risks and benefits of antidepressants and untreated maternal depression during pregnancy should be discussed with all female patients who have reproductive potential. Whenever possible, a pregnancy should be planned in consultation with a treating psychiatrist, who may wish to consult with a specialist in perinatal psychiatry. For women who are pregnant or planning to become pregnant, decisions about treatment for depression require weighing multiple benefits and risks for the woman as well as for the fetus. Making such decisions may require several discussions and will generally involve discussions with the patient's partner as well as her obstetrician.

Antidepressant medications carry some reported risks in pregnancy (see below), but so does untreated depression. Suicide risk, marital discord, the inability to engage in appropriate obstetrical care, and difficulty caring for other children must also be considered. There are also serious and well-characterized risks to the fetus of exposure to maternal major depressive disorder, including the possibility of low birth weight secondary to poor maternal weight gain (or frank weight loss) and increased risk of obstetrical complications such as premature delivery (748).

Antidepressant efficacy has not been determined for pregnant women, and questions remain as to whether medications have equivalent efficacy during pregnancy, compared with the nonpregnant state. Some safety data are available, but the findings often conflict, making data interpretation challenging and difficult to apply to the care of individual patients. Nevertheless, antidepressant medication should be considered and discussed as an option with pregnant women who have moderate to severe major depressive disorder.

For women who are in remission from major depressive disorder and receiving maintenance medication and/or for women deemed to be at high risk for a recurrence if the medication is discontinued, the risks of treatment with medications must also be weighed against the risks of alternative treatment options and untreated depression. Relapse rates for women with a history of major depressive disorder are high during pregnancy, especially if antidepressants are discontinued (749).

1. Risks of antidepressants during pregnancy

The impact of the duration and timing of antidepressant exposure during pregnancy requires further study. Wisner et al. (750) reviewed the risks associated with the use of antidepressants during pregnancy, and a growing body of complicated literature has followed. Overall, risk of teratogenicity with antidepressants following first trimester

exposure appears to be low, although some rare birth defects have been observed to occur at higher rates with use of specific SSRIs (751, 752). First-trimester paroxetine exposure has been associated with cardiac malformations, a finding that resulted in changes in FDA labeling for paroxetine from C to D (753); labeling changes have been made to all SSRI antidepressants with regard to this possibility when used during pregnancy. There have been conflicting results regarding whether first-trimester paroxetine exposure and cardiac teratogenicity are associated (754, 755). For fluoxetine, one study (756) found a higher incidence of three or more minor physical anomalies in infants exposed to fluoxetine than in a control group, and fetuses exposed to fluoxetine after 25 weeks' gestation had lower birth weights, which were associated with lower maternal weight gain. Although one case-control study reported a potential association between late antenatal SSRI use and the rare but serious condition of persistent pulmonary hypertension in the newborn (PPHN) (757), two subsequent retrospective chart review studies showed no such association (758, 759). An additional case-control study (760) showed a marginally significant increase in the relative risk of PPHN with SSRI use, but the estimated rate of PPHN occurrence was 1.5 per 1,000 births, which is less than the rate of 2.7 per 1,000 births reported by others (758) in non-SSRI exposed infants. Therefore, while many physicians are concerned about the reported association between SSRIs and PPHN, the preponderance of evidence from published studies on this topic does not support an association. Use of SSRIs may also be associated with prematurity (761, 762), although untreated depression and stress during pregnancy may also contribute to the risk of prematurity (748, 763). Some naturalistic studies and health care utilization studies suggest that antidepressants are associated with shorter length of gestation (761, 762), but there have been no randomized studies of the treatment of antenatal major depressive disorder that would adequately control for untreated maternal depression, antidepressant use, and confounding variables related to treatment selection. With late pregnancy antidepressant use, some but not all studies show a risk of medical complications such as prematurity and a transient neonatal withdrawal/adaptation syndrome (761, 764). The syndrome in the neonate appears to be associated with antidepressant use in the third trimester, has been reported in babies exposed in utero to TCAs and SSRIs, and includes transient symptoms such as jitteriness, tremor, difficulty with feedings, and other symptoms (764). Several studies, involving relatively small samples, have examined effects of antidepressant exposure during pregnancy on subsequent childhood behavior and development and found minimal (765) or no (766–768) effects on language, cognition, or motor or behavioral development independent of maternal depressed mood during pregnancy and the child's early life (766, 767).

2. *Implementation of pharmacotherapy during pregnancy*

No controlled trials inform the use of antidepressants during pregnancy. Dose requirements may change during pregnancy because of changes in volume of distribution, hepatic metabolism, protein binding, and gastrointestinal absorption. Pharmacokinetic changes in late pregnancy may result in lower blood levels, with clinical implications, although more study is needed to develop monitoring and dosing guidelines. The limited data in this area demonstrate that pregnant women metabolize TCAs and SSRIs more rapidly in late pregnancy (769–774).

A number of factors influence antidepressant choice during pregnancy. If a woman has had a history of a good response to or is already taking a particular antidepressant, it is logical to consider that antidepressant among first-line treatments in an effort to minimize the number of different medication exposures. Using a single agent is also preferable to using several medications concomitantly. Because paroxetine use is classified as having a higher level of risk than other SSRIs, it should not be considered a first-line treatment when selecting a new antidepressant for a pregnant patient. Fluoxetine has the longest half-life and is more likely to be demonstrated at high levels in newborns after in utero exposure. Sertraline has been demonstrated to have lower cord blood levels than other SSRIs, although the clinical significance of this is unknown (775). Although there are few data for bupropion and safety in pregnancy, its benefits for smoking cessation may make it especially useful in women who have major depressive disorder and who smoke cigarettes, as tobacco is a known teratogen. Given these data, it is recommended that consideration be given to using an antidepressant with some available safety information that has been studied in pregnant women. For women who discontinue medication during pregnancy and are deemed at risk for postpartum depression, medication can be restarted following delivery.

Electroconvulsive therapy is also recommended as a treatment option for major depressive disorder during pregnancy (239). The current literature supports the safety for mother and fetus, as well as the efficacy of ECT during pregnancy (239). The psychiatrist should consider ECT for pregnant patients with moderate to severe depression who are unresponsive to or unsuitable for pharmacotherapy, for pregnant patients with major depressive disorder with psychotic features, and for pregnant patients electing to use this modality as a matter of prefer-

ence after having weighed the relative risks and benefits of ECT and other treatment options. For details on the use of ECT during pregnancy, refer to *The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging (A Task Force Report of the American Psychiatric Association)* (239).

b. Postpartum depression

Major depressive disorder with postpartum onset is defined in DSM-IV-TR as a major depressive episode with onset within 4 weeks of delivery. However, the occurrence and course of major depressive disorder in childbearing women is heterogeneous, and definitions of postpartum depression may evolve with continued research (16, 776). In major depressive disorder with postpartum onset, anxiety symptoms are more prevalent than in major depressive disorder occurring at other times (777). It is not uncommon for women with postpartum depression to experience obsessions and/or compulsions, and obsessions may often involve thoughts of harming the baby, which must be differentiated from postpartum psychosis. Psychiatrists should provide psychoeducation about major depressive disorder to pregnant and postpartum women and their families to improve the detection of major depressive disorder during pregnancy and the postpartum period.

Several other psychiatric conditions may follow childbirth (778). The transient 7- to 10-day depressive condition referred to as "postpartum blues" is by definition too mild to meet the criteria for major depressive disorder and does not require medication. In addition to providing reassurance, psychiatrists should encourage mothers who experience postpartum blues to increase psychosocial support and obtain help with the care of the infant. Puerperal psychosis is a more severe disorder complicating one to two of 1,000 births. Although postpartum psychosis is rare, women with this disorder may have homicidal impulses toward the newborn; for this reason, careful assessment of homicidal as well as suicidal ideation, intention, and plans is important. Postpartum psychosis must always be treated as a psychiatric emergency, with hospitalization considered for the safety of the mother and baby (779). Many patients who have had episodes of this type ultimately prove to have bipolar disorder (780).

The woman's parenting skills for both the newborn baby and any other children in her care must be carefully assessed. Untreated maternal major depressive disorder, and specifically postpartum depression, have negative consequences for children, with adverse effects on attachment and child development (781, 782). Major depressive disorder can seriously interfere with the new mother's ability to provide physically and emotionally appropriate care for her baby and other children. The psychiatrist should work with the patient to develop a plan to manage this effect, such as enlisting family members to assist with child care.

Antidepressants are often prescribed for postpartum depression, according to the same principles delineated for other types of major depressive disorder, despite a limited number of controlled studies. Two placebo-controlled trials of SSRIs (fluoxetine and paroxetine) have been published for the treatment of postpartum depression, with fluoxetine appearing more efficacious than placebo and paroxetine being comparable to placebo on primary outcome measures of depressive symptoms (783, 784). Wisner et al. (785) did not find a difference in response and remission rates in a randomized controlled trial of sertraline versus nortriptyline for postpartum major depressive disorder. Open studies of other antidepressants in postpartum women suggest efficacy, although some studies included only a small number of participants (786). Paroxetine alone and paroxetine plus CBT both produced a significant change from baseline in one study, but there was no placebo-only group for comparison (787).

Patients and clinicians are often concerned about the risks of possible exposure to antidepressants during breast-feeding. These risks, however, must be weighed against the well-known, and at times profound, risks to the woman and her children of untreated postpartum depression. Mothers should be counseled regarding the relative risks and benefits when making these treatment decisions. Antidepressant medications are considered compatible with breast-feeding, but long-term data are not available regarding risks and benefits. Although there have been some suspected case reports of adverse effects in breast-feeding infants exposed to maternal antidepressants, most studies show low levels of exposure via breast milk, with the exception of fluoxetine, which appears to have a dose-related risk for detectable levels in infant sera (788, 789). At this time, there are no studies which have determined a "safe" amount and duration of antidepressant exposure in the fetus and newborn. However, exposure to antidepressants via breast milk is considered substantially lower than in-utero exposure. Women who elect to breast-feed while taking antidepressants should be supported in doing so, given the widely known health benefits (e.g., immune system effects) to infants who are breast-fed. Similarly, women who elect to bottle-feed should also be supported in this decision. Some women will not accept treatment with antidepressant medication while they are breast-feeding. Depression-focused psychotherapy can be recommended instead.

7. Family history

Major depressive disorder is one and one-half to three times as common among those with a first-degree biological relative affected with the disorder as in the general population. In addition, the rates of depression, anxiety, and other disorders are increased more than two- to six-fold in the offspring of depressed parents. A family history of depression is associated with an earlier age at onset of depression (790), and children of depressed parents are more likely to have depression with a chronic and recurrent course (791). Furthermore, a family history of recurrent major depressive disorder increases the chances that the patient's own illness will be recurrent and that the patient will not fully recover between episodes (792). A family history of bipolar I disorder, bipolar II disorder, or acute psychosis probably increases the chances that the patient's own major depressive disorder is a manifestation of bipolar rather than unipolar depression, and that antidepressant medication therapy may incite a switch to mania (793). Patients with such a family history should be questioned particularly closely regarding a prior history of mania or hypomania and should be carefully observed for signs of a switch to mania during treatment with antidepressant medication.

There are no real predictors of response to individual antidepressants, yet in the absence of other information clinicians sometimes rely on family history of therapeutic benefit to select a specific medication for a family member. Although it does not have specific support in the literature, this practice appears reasonable.

C. TREATMENT IMPLICATIONS OF CO-OCCURRING GENERAL MEDICAL CONDITIONS

In patients with co-occurring medical conditions, there is a higher prevalence of major depressive disorder than in the general population. Furthermore, co-occurring medical conditions in patients with major depressive disorder are associated with poorer outcome (794, 795). A number of medical conditions are known to cause mood symptoms, such as stroke, hypothyroidism, carcinoma of the pancreas, and many others. Apart from directly causing depressive symptoms, debilitating, painful, and chronic medical conditions often constitute an ongoing stressor that predisposes patients to depressive episodes. Nevertheless, a depressive episode, in any context, is never a "normal" response to illness and consequently warrants treatment.

In addition to the increased risk of major depressive disorder with general medical conditions, depressive episodes increase the risk of certain general medical conditions, such as heart disease. (796). Due to the interrelationship between depression and medical illness, it is very important to recognize and treat depressive symptoms in medically ill patients, and vice versa. The psychiatrist should also attend to the potential for interactions between antidepressants and the co-occurring medical conditions as well as any nonpsychiatric medications that the patient may be taking.

1. Hypertension

The presence of treated or untreated hypertension may influence the choice of an antidepressant, as a few antidepressant medications have been associated with increases in blood pressure. With SNRIs such as venlafaxine and duloxetine, dose-dependent elevations in blood pressure are usually mild, although more severe hypertension has also been observed (166, 797). However, another study found no increase in hypertension with duloxetine dosed up to 80 mg/day (798). Hypertension induced by SNRIs may respond to a decrease in the medication dose, or an alternative antidepressant medication may be considered. Alternatively, for a patient with well-controlled depressive symptoms, it may be preferable to add an antihypertensive agent rather than risk a depressive relapse or recurrence with medication tapering.

Antihypertensive agents and antidepressant medications may interact to either intensify or counteract the effect of the antihypertensive therapy (799). The action of antihypertensive agents that block alpha receptors (e.g., prazosin) may be intensified by antidepressant medications that block these same receptors, notably the TCAs and trazodone. Tricyclic antidepressants may antagonize the therapeutic actions of guanethidine, clonidine, or alpha-methyldopa. Concomitant antihypertensive treatment, especially with diuretics, increases the likelihood that TCAs, trazodone, or MAOIs will induce symptomatic orthostatic hypotension.

Side effects of antihypertensive agents, such as fatigue or sexual dysfunction, may also confound the evaluation and interpretation of depressive symptoms. It has also been thought that beta-blockers, especially propranolol, may account for depressive symptoms in some patients, but this association has been questioned (700, 701).

2. Cardiac disease

Depression increases the risk of cardiovascular disease (800). In addition, patients who are depressed following a myocardial infarction have an increased rate of mortality, compared with patients without depression (801–803). Following an acute myocardial infarction, the decreased survival rates of depressed patients may in part be due to

lower heart rate variability in these patients, compared with nondepressed patients (804). Particularly in patients with a history of major depressive disorder (805), there is evidence that the depressive symptoms associated with cardiac illness respond to antidepressants (717, 806, 807). However, studies in which the attempt has been made to influence cardiac-related mortality through treatment of depression have shown mixed results (808–811).

A depressed patient with a history of a cardiac problem should be monitored for the emergence of cardiac symptoms, ECG changes, persistent tachycardia, or orthostatic blood pressure decrements. Consultation with the patient's cardiologist before and during antidepressant medication treatment may be advisable, especially for patients who have recently had a myocardial infarction. Increases in heart rate and blood pressure may be associated with the use of agents with noradrenergic properties such as SNRIs and stimulants; thus, changes in heart rate and blood pressure should be assessed after treatment with these agents is instituted in patients with coronary artery disease, hypertension, or congestive heart failure. Although TCAs have been used effectively to treat major depressive disorder in patients with some forms of ischemic heart disease (812), psychiatrists should take particular care in using TCAs for patients with a history of ventricular arrhythmia, subclinical sinus node dysfunction, conduction defects (including asymptomatic conduction defects), prolonged QT intervals, or a recent history of myocardial infarction (184, 185, 813–818). Selective serotonin reuptake inhibitors, SNRIs, and bupropion appear to be safer for patients with preexisting cardiac disease; several SSRIs have been used safely in patients with cardiac disease in large clinical trials (807, 809, 810, 819). Electroconvulsive therapy can also be used safely in individuals with cardiac disease or arrhythmias, although specialist consultation and modifications in ECT technique or anesthesia may be indicated (239, 245, 820–822). Monamine oxidase inhibitors do not adversely affect cardiac conduction, rhythm, or contraction but may induce orthostatic hypotension and have risks relating to drug-food and drug-drug interactions.

3. Stroke

Depression is observed in approximately one-third to one-half of individuals in the weeks to months following a stroke, with a substantial proportion developing major depressive disorder (334, 823, 824). Although conclusions of meta-analyses are mixed (825, 826), some research suggests that antidepressant treatment immediately following a stroke may reduce rates of depression (334) and possibly mortality (827). Among psychotherapeutic approaches to preventing depression after stroke, problem-solving therapy has been best studied, but findings are inconsistent (334, 825).

When depression develops after a stroke, it has detrimental effects on quality of life (823). In addition, the presence of depression 1 month following a stroke has been associated with an increase in subsequent mortality (828). Use of screening tools such as the PHQ-9 may help to identify depressive episodes after stroke (829), and care management may improve outcomes once poststroke depression is recognized (830). Psychotherapies have not been well studied as treatments for poststroke depression; however, a meta-analysis of randomized trials that have been conducted did not show efficacy (825). Findings on the therapeutic effects of antidepressants in post-stroke depression have been mixed, perhaps due to the substantial heterogeneity of study populations and designs (831, 832). Although a meta-analysis did not show any difference in the rate of depressive remission with antidepressant treatments compared with placebo (832), patients receiving an antidepressant did show more improvement in depressive symptoms (831, 832) and a greater proportion were classified as treatment responders (831). Individual randomized controlled trials have shown therapeutic benefits for several SSRIs, including fluoxetine, sertraline, and citalopram (833–836), and for the TCA nortriptyline (837, 838); however, not all studies have shown benefit for some of these agents (837, 839–841). Nevertheless, for individuals with poststroke depressive symptoms, a trial of antidepressant therapy may be considered, with SSRIs being better tolerated and having fewer contraindications in this older and more medically ill population (842, 843). However, in individuals who are receiving concomitant treatment with anticoagulant (e.g., warfarin) or antiplatelet (e.g., dipyridamole, clopidogrel, aspirin) medications, it is important to consider the potential for an increased bleeding risk due to drug-drug interactions with antidepressants (844, 845).

4. Parkinson's disease

Major depressive disorder occurs to some degree in 40%–50% of patients with Parkinson's disease. Patients with Parkinson's disease experience alterations of serotonergic and noradrenergic systems that may induce depression. There is no evidence favoring any particular antidepressant medication from the standpoint of therapeutic efficacy and safety for patients with Parkinson's disease complicated by major depressive disorder (846). A meta-analysis of placebo-controlled studies identified a clear benefit for both active treatment and placebo, but it did not find differences between them (847). Although SSRIs

can be used, there is some risk of worsening of Parkinson's disease symptoms (increases in "off" time and exacerbation of tremor) with agents that are primarily serotonergic (848). Bupropion, in contrast, exerts a beneficial effect on the symptoms of Parkinson's disease in some patients but may also induce psychotic symptoms, perhaps because of its agonistic action in the dopaminergic system (849). Noradrenergic agents and SNRIs may also be preferable to SSRIs. Nonselective MAOIs (e.g., tranylcypromine, phenelzine, isocarboxazid) may adversely interact with L-dopa products (850). Selegiline, also known as L-deprenyl, is a selective type B MAOI recommended in the treatment of Parkinson's disease. Selegiline loses its specificity for MAO B in doses greater than 10 mg/day. As a result, it may induce serotonin syndrome when given in higher doses in conjunction with serotonin-enhancing antidepressant medications. The theoretical benefits of the antimuscarinic effects of some of the tricyclic agents in the treatment of patients with major depressive disorder with Parkinson's disease are offset by the memory impairment that may result. Amoxapine, an antidepressant medication with dopamine-receptor-blocking properties, should be avoided for patients who have Parkinson's disease. Lithium may, in some instances, induce or exacerbate parkinsonian symptoms. Electroconvulsive therapy exerts a transient beneficial effect on the symptoms of idiopathic Parkinson's disease in many patients (851, 852); however, it might occasionally worsen L-dopa-induced dyskinesias and induce a transient interictal delirium (853), which necessitates reductions in doses of dopamine agonist medications (239).

5. Epilepsy

The prevalence of depression in individuals with epilepsy appears to be increased in secondary and tertiary care center samples, although in population-based studies this increase is not well established (854). On the other hand, major depressive disorder significantly increases the risk of unprovoked seizures even after the adjustment of age, sex, length of medical follow-up, and medical therapies for depression (855). In addition, some antidepressant drugs, such as TCAs and bupropion, lower the seizure threshold and have a dose-dependent epileptogenic potential. This seizure risk is intermediate for immediate-release formulations of bupropion, maprotiline, and TCAs (in particular, clomipramine) and low for sustained-release formulations of bupropion (17, 197, 856).

Major depressive disorder in patients with seizure disorders can usually be safely and effectively managed according to the same principles outlined for patients without seizures. In particular, SSRIs and SNRIs are not likely to increase the risk of developing seizures (856–858). However, blood levels of TCAs may be increased by several antiepileptic drugs, increasing the side-effect burden of the anticholinergic and other side effects of tricyclics (859).

Some anticonvulsants appear useful for treatment and prophylaxis of mood disorders (e.g., carbamazepine, valproate, lamotrigine). Thus, in patients with depression and epilepsy, consideration can be given to concomitant prescription of an anticonvulsant (or elevating the dose of an existing anticonvulsant). Nevertheless, anticonvulsant compounds may also have a negative effect on mood for some patients (859). For example, barbiturates and possibly vigabatrin have been associated with an increased risk for depression (860). In addition, a recent FDA statement noted that increased rates of depression and suicide risk may be associated with anticonvulsants (861).

6. Obesity

Many individuals with major depressive disorder will be overweight or obese, given the high prevalence of excess weight in the general population (862). In addition, rates of depression may be increased in obese individuals, particularly among women and in those with a body mass index (BMI) greater than 40 (863). Individuals with obesity resulting from binge eating disorder also have higher rates of depression (170). In the subgroup of patients with atypical depression, increased eating and weight gain are symptomatic of the depressive disorder (864). For other patients, the lack of motivation and energy that occur with depression can make it difficult to maintain an exercise regimen or nutritional dietary habits. In addition, treatment with many antidepressant medications appears to lead to weight gain (865) and also makes it more difficult to lose weight in a structured weight management program (866).

In treating individuals with major depressive disorder who are overweight or obese, the effects of treatment on weight should be considered in selecting a therapeutic approach. If pharmacotherapy is used, the selection of an antidepressant medication should include consideration of its relative tendency to contribute to weight gain, which is generally greatest with mirtazapine, TCAs (tertiary TCAs more so than secondary TCAs), and MAOIs and less prominent with SSRIs and SNRIs (865). Bupropion is generally weight neutral and has been associated with modest weight reduction when used to treat major depressive disorder in obese adults (867, 868). Longitudinal monitoring of weight, either by direct measurement or patient report, can permit monitoring of BMI, as well as early intervention if weight gain becomes a problem with

antidepressant treatment. Patients' concerns about weight gain may also contribute to poor adherence, and monitoring of weight can facilitate such discussions. The impact of weight on medication dosing should also be considered. In one study, greater relative body weight was associated with a lesser likelihood of response to a fixed dose trial of an antidepressant (869), perhaps suggesting a need for increases in medication dose with increasing body weight.

Psychotherapeutic approaches to treatment avoid the potential for medication-induced weight gain and may also have modest benefits in weight management. Cognitive-behavioral therapy has shown efficacy in the treatment of binge eating disorder (170, 870) and could potentially be used in addressing obesity (871) and medication-induced weight gain (872).

The increasing use of surgical treatments for obesity also has implications for the treatment of patients with major depressive disorder. Depression is common among bariatric surgical candidates and, in and of itself, is not a contraindication for surgery (873–877). Long-term follow-up studies show improvements in co-occurring general medical conditions (878), as well as decreases in depressive symptoms and improved quality of life with weight loss (879–881). However, weight loss after surgery may be less pronounced in individuals with a lifetime diagnosis of major depressive disorder (882) or in those with severe psychiatric illness that has required hospitalization (883). Close follow up is important following bariatric surgery in order to assess for changes in psychiatric symptoms, assist patients in the psychological and psychosocial adaptation to weight loss, and adjust medication regimens. Particularly following jejunoileal bypass or biliopancreatic diversion, but also following gastric bypass procedures, altered dissolution (884) and absorption of medication may require adjusting the dose of medication or changing from a slow-release to an immediate-release formulation (875).

7. Diabetes

Diabetes mellitus is common in the general population, particularly in overweight or obese individuals (885). However, it is not clear whether an association exists between diabetes and major depressive disorder, as meta-analyses and epidemiologic studies yield mixed results (886–888). Some patients may have reduced adherence to diet and medications when depressed (889), but there are inconsistent findings on whether successful treatment of depression (with medication, psychotherapy, and/or collaborative care) improves glycemic control (889–896). However, when initiating antidepressant therapy or making significant dosing adjustments, it is useful to collaborate with the patient's primary care physician in monitoring diabetic control because fluctuations in fasting blood glucose may occur. Some evidence suggests that use of TCAs may be associated with worsened glycemic control, and other antidepressants (such as SSRIs) may be preferable to TCAs for patients with diabetes (896, 897).

8. Sleep apnea

The possible contribution of obstructive sleep apnea (OSA) to depressive symptoms is an important consideration, particularly in patients who are obese, report excessive daytime sleepiness, or have treatment-resistant depressive symptoms. Symptoms such as fatigue and poor sleep quality can occur in sleep apnea as well as in major depressive disorder, requiring a careful assessment to distinguish whether either or both disorders are present. Underrecognition of OSA is common, and rates of OSA appear to be increasing with the increasing prevalence of obesity (898). Although the prototypical sleep apnea patient is likely to be obese with a history of snoring, sleep apnea may still be present even in the absence of these findings (899). Individuals with OSA or excessive daytime sleepiness appear to have greater rates of depression than comparison groups (900–902), although the rates of depressive symptoms and major depressive disorder diagnosis fluctuate across studies (903). In addition, epidemiological findings suggest an increasing likelihood of depression with increasing sleep-related breathing disorder severity (904). With initiation of continuous positive airway pressure treatment, improvement in OSA symptoms has been associated with decreased depressive symptoms (905, 906), in addition to reductions in OSA-associated health risks (898). Consequently, recognition and treatment of OSA is important among individuals with major depressive disorder. Identification of OSA is also important to treatment planning, as use of sedating medications can exacerbate OSA and worsen daytime sleepiness, with associated complications (907).

9. Human immunodeficiency virus and hepatitis C infections

According to the Centers for Disease Control and Prevention, more than one million individuals in the United States were living with HIV infection by the end of 2003 (908), with increased rates among individuals with psychiatric disorders, including substance use disorders (909). Estimates suggest that at least one-fifth of infected individuals have unrecognized infection (910), necessitating increased efforts to identify HIV infection (911), given the availability of effective treatment (912). Consequently, clinicians treating patients with major depressive disorder should consider screening for HIV.

Rates of major depressive disorder are increased among individuals with HIV infection, compared with HIV-negative individuals (913). When treating major depressive disorder in patients who also have HIV, antidepressant medications can be used safely and effectively (914, 915), although high placebo response rates and high study attrition rates have sometimes confounded interpretation of research findings (916, 917). When antidepressants are used, SSRIs are better tolerated than TCAs (918, 919). In individuals who are receiving treatment with antiretroviral agents, it is important to check for potential drug-drug interactions when choosing a medication regimen (920). Significant interactions can also occur if St. John's wort is taken by patients receiving antiretroviral medications. Although few studies have been conducted in patients who meet diagnostic criteria for major depressive disorder, individual and group psychotherapies using interpersonal, cognitive-behavioral, and psychoeducational approaches have also been associated with reductions in depressive symptoms among patients with HIV infection (316, 921–926).

Persons with mental illness also have elevated rates of infection with hepatitis C (927), and infection with hepatitis C is commonly present in individuals with HIV infection (928). Among individuals with hepatitis C, depressive symptoms are common, and many patients fully meet the criteria for major depressive disorder (929). Treatment of hepatitis C with interferon appears to be associated with a further increase in the risk for depression, although findings vary depending upon the study population, concomitant medications (e.g., ribavirin), and the type of interferon used for therapy (930, 931). The increase in depressive symptoms with interferon treatment may also be more prominent in patients with greater levels of pretreatment depression (932). This suggests a need for careful monitoring if patients with current major depressive disorder are administered interferon, particularly since many patients treated with interferon have unrecognized or insufficiently treated depression (933). Studies in which antidepressant medications were administered concomitantly with interferon have shown inconsistent prophylactic effects (934, 935). However, antidepressant therapy does seem to be effective when used to treat depression that develops in the course of interferon therapy for hepatitis C infection (936, 937). Consequently, major depressive disorder should not be viewed as a contraindication to the treatment of hepatitis C infection, particularly given the severe long-term hepatic complications associated with chronic infection (938).

10. Pain syndromes

Pain syndromes and major depressive disorder frequently co-occur. Although the reported prevalence of pain among depressed patients varies with cultural differences and study design, one-half to two-thirds of depressed individuals will typically note some type of pain (702, 939–941). Conversely, in primary care settings, individuals with pain symptoms are about twice as likely to be depressed as those without pain, and the rates of depression are further increased if pain is chronic or involves multiple types of pain (940, 942). It is important to note that individuals with co-occurring pain and depression tend to have worse treatment outcomes and poorer overall functioning than those with either condition alone (940, 942–944). Consequently, every patient with depression should be assessed for the presence, nature, location, and severity of pain complaints.

Overall, antidepressant treatment has been associated with reductions in pain symptoms among individuals with psychogenic or somatoform pain disorders (945). However, among trials of second-generation antidepressants in individuals with co-occurring pain and depression, duloxetine, venlafaxine, and paroxetine seem to be of comparable but relatively minor benefit (939, 946, 947).

Neuropathic pain is commonly associated with diabetic peripheral neuropathy but may also have other etiologies such as postherpetic neuralgia. For neuropathic pain in general, evidence-based guidelines recommend the use of TCAs or SNRIs (948, 949). Of the antidepressant medications, TCAs have been found to be most effective in decreasing pain associated with both postherpetic neuralgia (950, 951) and diabetic neuropathy (949, 952) but have no apparent effect on HIV-associated neuropathic pain (949). Given the greater tolerability of SNRI antidepressants, these agents may sometimes be chosen before a TCA for a patient with co-occurring depression and neuropathic pain. In addition, if a TCA is used, therapeutic drug monitoring may be helpful, given the wide variability of TCA blood levels across individuals (953).

Similar effects have been found for the use of antidepressants to prevent migraine and tension-type headaches. In patients with and without co-occurring depression, TCAs show greater efficacy than SSRIs (954, 955), but SNRIs also have some evidence for efficacy (956, 957). In individuals with tension-type headaches, addition of stress management therapy may augment the effects of TCA treatment (958).

Antidepressant treatment is also recommended for individuals with fibromyalgia, as it is associated with reductions in pain and often leads to improvements in function, with the best evidence available for amitriptyline (959). Beneficial effects are observed in those with or without co-occurring major depressive disorder (960–962). Although evidence from controlled trials is more limited for nonpharmacological approaches than for antidepressant treatment, education, exercise, and CBT are generally rec-

ommended for the treatment of fibromyalgia in combination with antidepressant medication (963, 964).

In the context of rheumatoid arthritis, antidepressant medications also appear to be effective in reducing pain as well as treating depressive symptoms (965–967). Evidence for psychosocial treatment is less consistent, with mindfulness meditation and emotion regulation therapy being associated with reduced pain and enhanced coping in individuals with rheumatoid arthritis and depression (968), but CBT having mixed results (966, 968). In individuals with co-occurring depression and osteoarthritis, collaborative depression care has been associated with reduced pain severity, improved function, and enhanced quality of life in those with low pain scores at baseline but had no effect when compared with usual treatment in those with severe arthritis pain (969, 970).

For individuals with chronic low back pain, there are conflicting opinions about the utility of antidepressant medications in reducing pain or improving function, even in the presence of co-occurring depression (971, 972). Nevertheless, antidepressant medications may still be indicated to treat depression on the basis of individual circumstances.

Since depressed patients with concurrent pain are often treated by primary care physicians and other medical specialists with a variety of potent analgesic medications, including narcotics, psychiatrists treating such patients are advised to be in contact with these other physicians initially and on a regular ongoing basis as indicated. The purposes of such contacts are to review the entire treatment plan, to assure that all prescribing physicians are aware of the full extent of pharmacological interventions, to coordinate specific prescribing areas and responsibilities so that patients do not receive prescriptions for the same medications or have their doses for given medications adjusted by several different prescribing clinicians, and to set up a mechanism and plan whereby all prescribing clinicians consistently keep one another informed about changes in their treatment plans and prescriptions.

11. Obstructive uropathy

Enlarged prostate size and other causes of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects. For this reason, tertiary amine TCAs are best avoided in these patients. Benzodiazepines, trazodone, and MAOIs may also retard bladder emptying. The antidepressant medications with the least propensity to do this are SSRIs, SNRIs, and bupropion. If a TCA is chosen, the secondary amine desipramine is the least likely to cause urinary hesitancy or retention.

12. Glaucoma

Medications with anticholinergic potency may precipitate acute narrow-angle glaucoma in susceptible individuals (i.e., those with shallow anterior chambers) (973). Patients with glaucoma receiving local miotic therapy may be treated with antidepressant medications, including those possessing anticholinergic properties, provided that their intraocular pressure is monitored during antidepressant medication treatment. Prescription of agents lacking anticholinergic activity avoids this risk. Other agents sometimes used in psychiatry, e.g., topiramate and related sulfa-based medications, may cause acute angle closure glaucoma by ciliary body edema, a different mechanism (974).

Part B

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV. DISEASE DEFINITION, EPIDEMIOLOGY, NATURAL HISTORY, AND COURSE

A. DISEASE DEFINITION

The DSM-IV-TR criteria for major depressive episode and major depressive disorder are listed in Table 11. The cardinal feature of a major depressive episode is either a depressed mood or loss of interest or pleasure in usual activities that persists over a period of at least 2 weeks and is

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	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). 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) 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) 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 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6. Fatigue or loss of energy nearly every day 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) 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 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 B. The symptoms do not meet criteria for a mixed episode. C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. 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). 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.
Major depressive disorder, single episode	A. Presence of a single major depressive episode. 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. C. There has never been a manic episode, a mixed episode, or a hypomanic episode.

(continued)

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

Diagnosis	Criterion/Symptom Description
Major depressive disorder, recurrent	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). 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. C. There has never been a manic episode, a mixed episode, or a hypomanic episode

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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 catalepsy (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 individual 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 significant 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 treating 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 ± 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 experienced 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 ± 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 naturalistically, 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 individuals (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.

Electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, TMS, other electromagnetic stimulation therapies) should be compared. Approaches to reducing cognitive side effects of ECT, speeding response to ECT, or determining the indications and best methods for maintenance ECT could improve patient care. More research is also needed on the optimal approaches (e.g., treatment schedule, stimulation parameters) for delivering newer stimulation therapies. Additional research on light therapy would be helpful, including determining its effectiveness as adjunctive treatment in nonseasonal major depressive disorder or as a primary treatment for seasonal major depressive disorder in the maintenance phase. Given patients' frequent use of complementary therapies, additional research on these therapies, including acupuncture, is warranted. Further study of exercise in acute and maintenance treatment of depression would also be useful, including assessment of the benefits of exercise in minimizing side effects of the other therapies and in optimizing health, functioning, and quality of life.

In time, brain imaging, genomics, proteomics, and other recent advances in neuroscience should help us "carve nature along its joints," allowing major depressive disorder to be broken into discrete diseases with defined and personalized treatments. In the meantime, clinical investigation focused on existing and novel treatment strategies remains essential.

Appendix

EDUCATIONAL RESOURCES FOR PATIENTS AND FAMILIES

Academy of Cognitive Therapy
http://www.academyofct.org

California Teratogen Information Service and Clinical Research
Tel: 1–800–532–3749 (CA only)
Tel: (610) 543–2131
http://www.otispregnancy.org

ConsumerLab.com
Tests herbal and vitamin products for purity and posts the results on the Web
http://www.consumerlab.com

Depression After Delivery, Inc.
91 East Somerset Street
Raritan, NJ 08869
Tel: (800) 944–4773
http://www.depressionafterdelivery.com

Depression and Bipolar Support Alliance
730 Franklin Street
Suite 501
Chicago, IL 60610–7224
Tel: (312) 642–0049
Tel: (800) 826–3632
http://www.ndmda.org

Healthy Minds, Healthy Lives
American Psychiatric Association
http://www.healthyminds.org

International Foundation for Research and Education on Depression
2017-D Renard Court
Annapolis, MD 21401
Tel: (410) 268–0044
http://www.ifred.org

International Society of Interpersonal Psychotherapy
http://www.interpersonalpsychotherapy.org

KidsHealth.org
http://www.kidshealth.org

Massachusetts General Hospital Women's Mental Health Program
http://www.womensmentalhealth.com

Mental Health America
2000 N. Beauregard Street
6th Floor
Alexandria, VA 22311
Tel: (703) 684–7722
Tel: (800) 969–6MHA (6642)
TTY Line: (800) 433–5959
http://www.nmha.org

MentalHelp.net
http://www.mhnet.org

Motherisk.com
Database maintained by the Toronto Hospital for Sick Children
http://www.motherisk.com

NARSAD
60 Cutter Mill Road
Suite 404
Great Neck, NY 11021
Tel: (516) 829–0091
http://www.narsad.org

National Alliance on Mental Illness
Colonial Place Three
2107 Wilson Blvd., Suite 300
Arlington, VA 22201
Tel: (703) 524–7600
Help Line: (800) 950-NAMI [6264]
http://www.nami.org

National Center for Complementary and Alternative Medicine
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892
http://nccam.nih.gov/

National Institute of Mental Health
Depression Information Program
6001 Executive Boulevard
Room 8184, MSC 9663
Bethesda, MD 20892–9663
Tel: (301) 443–4513
TTY Line: (301) 443–8431
http://www.nimh.nih.gov/health/topics/depression/index.shtml

National Institute of Mental Health Mental Health Topics
http://www.nimh.nih.gov/health/topics/index.shtml

National Institute of Mental Health Public Information and Communications Branch
6001 Executive Boulevard
Room 8184, MSC 9663
Bethesda, MD 20892
Tel: (866) 615–6464
http://www.nimh.nih.gov/publicat/index.cfm

National Library of Medicine
U.S. government online repository of articles published in peer-reviewed medical journals
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

Postpartum Support International
http://postpartum.net

Substance Abuse and Mental Health Services Administration's National Mental Health Information Center
http://mentalhealth.samhsa.gov/

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American Academy of Neurology
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American Association of Emergency Psychiatry
American Geriatrics Society
American Group Psychotherapy Association
American Mental Health Counselors Association
American Neuropsychiatric Association
Association for Behavior and Cognitive Therapy
Association of Family Psychiatrists
Canadian Psychiatric Association
Community Mental Health Council, Inc.
National Association of Social Workers
Society for Adolescent Medicine
World Federation for Mental Health

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REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the references:

[A] *Randomized double-blind clinical trial.* A study of an intervention in which subjects are prospectively followed over time, there are treatment and control groups, subjects are randomly assigned to the two groups, both the subjects and the investigators are blind to the assignments.

[A–] *Randomized clinical trial.* Same as above but not double-blind.

[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.

[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.

[D] *Case-control study.* A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.

[E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.

[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.

[G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

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