PRACTICE GUIDELINE FOR THE
Treatment of Patients With Major Depressive Disorder
Second Edition

WORK GROUP ON MAJOR DEPRESSIVE DISORDER

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Originally published in April 2000. This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (http://www.guideline.gov/), this guideline can no longer be assumed to be current. A third edition of this guideline is in development; publication is expected in December 2009. The September 2005 Guideline Watch associated with this guideline provides additional information that has become available since publication of the guideline, but it is not a formal update of the guideline.

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STATEMENT OF INTENT

The American Psychiatric Association (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 judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

This practice guideline was approved in January 2000 and published in April 2000.

GUIDE TO USING THIS PRACTICE GUIDELINE

This practice guideline uses available evidence to develop treatment recommendations for the care of adult patients with major depressive disorder. This guideline contains 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 contains the treatment recommendations for patients with major depressive disorder. Section I is the summary of treatment recommendations, which includes the main treatment recommendations, along with codes that indicate the degree of clinical confidence in each recommendation. Section II is a guide to the formulation and implementation of a treatment plan for the individual patient. This section includes all of the treatment recommendations. Section III, "Specific Clinical Features Influencing the Treatment Plan," discusses a range of clinical conditions that could alter the general recommendations discussed in Section II.

Part B, "Background Information and Review of Available Evidence," will be useful to understand, in detail, the evidence underlying the treatment recommendations of Part A. Section IV provides an overview of DSM-IV criteria, prevalence rates for major depressive disorder, and general information on its natural history and course. Section V is a structured review and synthesis of published literature regarding the available treatments for major depressive disorder.

Part C, "Future Research Needs," draws from the previous sections to summarize those areas in which better 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://www.psych.org/psych_pract/pg/reviewform.cfm.

DEVELOPMENT PROCESS

This document is a practical guide to the management of major depressive disorder for adults over the age of 18 and represents a synthesis of current scientific knowledge and rational clinical practice. This guideline strives to be as free as possible of bias toward any theoretical posture, and it aims to represent a practical approach to treatment. Studies were identified through an extensive review of the literature by using MEDLARS for the period 1971–1999. The key words used were affective disorder, major depression, depressive disorder, seasonal affective disorder, melancholia, unipolar depression, endogenous depression, dysthymic disorder, dysthymia, postpartum depression, pseudodementia, antidepressant medications, tricyclic antidepressive agents, monoamine oxidase inhibitors, lithium, and electroconvulsive therapy and included the concepts of melancholia, neurotic depression, and major depression. In addition, the key words for the psychotherapy search were psychotherapy (not otherwise specified); behavior therapy, including aversive therapy, biofeedback (psychology), cognitive therapy, desensitization (psychologic), implosive therapy, and relaxation techniques (meditation); psychoanalytic therapy, including existentialism, free association, transactional analysis, psychotherapy (brief); and psychotherapy (group), including family therapy and marital therapy.

Major review articles and standard psychiatric texts were consulted. The Agency for Healthcare Policy Research *Evidence Report on Treatment of Depression—Newer Pharmacotherapies* (1) was reviewed in its entirety. Review articles and relevant clinical trials were reviewed in their entirety; other studies were selected for review on the basis of their relevance to the particular issues discussed in this guideline. Definitive standards are difficult to achieve, except in narrow circumstances in which multiple replicated studies and wide clinical opinion dictate certain forms of treatment. In other areas, the specific choice among two or more treatment options is left to the clinical judgment of the clinician.

The recommendations are based on the best available data and clinical consensus with regard to the particular clinical decision. The summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. In addition, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

INTRODUCTION

This guideline seeks to summarize the specific forms of somatic, psychotherapeutic, psychosocial, and educational treatments that have been developed to deal with major depressive disorder. It begins at the point where the psychiatrist has diagnosed an adult patient as suffering from major depressive disorder, according to the criteria defined in DSM-IV, and has medically evaluated the patient to ascertain the presence of alcohol or substance use disorder or other somatic factors that may contribute to the disease process (e.g., hypothyroidism, pancreatic carcinoma) or complicate its treatment (e.g., cardiac disorders). The purpose of this guideline is to assist the physician faced with the task of implementing specific antidepressant treatment(s). It should be noted that many patients have coexisting conditions and their difficulties cannot be described with one DSM diagnostic category. The psychiatrist should consider, but not be limited to, the treatment guidelines for a single diagnosis. For patients found to have depressive symptoms within the context of bipolar disorder, the psychiatrist should refer to the *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (2).

This document concerns patients 18 years of age and older. Some comments regarding the treatment of major depressive disorders in children and adolescents can be found in Section III.B.5., along with more definitive references.

PART A:
TREATMENT RECOMMENDATIONS FOR PATIENTS WITH MAJOR DEPRESSIVE DISORDER

I. SUMMARY OF TREATMENT RECOMMENDATIONS

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 regarding the recommendation:

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

Successful treatment of patients with major depressive disorder is promoted by a thorough assessment of the patient [I]. Treatment consists of an acute phase, during which remission is induced; a continuation phase, during which remission is preserved; and a maintenance phase, during which the susceptible patient is protected against the recurrence of subsequent major depressive episodes. Psychiatrists initiating treatment for major depressive disorder have at their disposal a number of medications, a variety of psychotherapeutic approaches, electroconvulsive therapy (ECT), and other treatment modalities (e.g., light therapy) that may be used alone or in combination. The psychiatrist must determine the setting that will most likely ensure the patient's safety as well as promote improvement in the patient's condition [I].

A. PSYCHIATRIC MANAGEMENT

Psychiatric management consists of a broad array of interventions and activities that should be instituted by psychiatrists for all patients with major depressive disorder [I]. Regardless of the specific treatment modalities selected, it is important to continue providing psychiatric management through all phases of treatment. The specific components of psychiatric management that must be addressed for all patients include performing a diagnostic evaluation, evaluating safety of the patient and others, evaluating the level of functional impairments, determining a treatment setting, establishing and maintaining a therapeutic alliance, monitoring the patient's psychiatric status and safety, providing education to patients and families, enhancing treatment adherence, and working with patients to address early signs of relapse.

B. ACUTE PHASE

1. Choice of an initial treatment modality

In the acute phase, in addition to psychiatric management, the psychiatrist may choose between several initial treatment modalities, including pharmacotherapy, psychotherapy, the combination of medications plus psychotherapy, or ECT [I]. Selection of an initial treatment modality should be influenced by both clinical (e.g., severity of symptoms) and other factors (e.g., patient preference) (Figure 1).

a) Antidepressant medications

If preferred by the patient, antidepressant medications may be provided as an initial primary treatment modality for mild major depressive disorder [I]. Antidepressant medications should be provided for moderate to severe major depressive disorder unless ECT is planned [I]. A combination of antipsychotic and antidepressant medications or ECT should be used for psychotic depression [I].

b) Psychotherapy

A specific, effective psychotherapy alone as an initial treatment modality may be considered for patients with mild to moderate major depressive disorder [II]. Patient preference for psychotherapeutic approaches is an important factor that should be considered in the decision. Clinical features that may suggest the use of psychotherapeutic interventions include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, or a comorbid axis II disorder [I].

c) Psychotherapy plus antidepressant medications

The combination of a specific effective psychotherapy and medication may be a useful initial treatment choice for patients with psychosocial issues, interpersonal problems, or a comorbid axis II disorder together with moderate to severe major depressive disorder [I]. 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 treatments may also warrant combined treatment modalities.

d) Electroconvulsive therapy

ECT should be considered for patients with major depressive disorder with a high degree of symptom severity and functional impairment or for cases in which psychotic symptoms or catatonia are present [I]. ECT may also be the treatment modality of choice for patients in whom there is an urgent need for response, such as patients who are suicidal or refusing food and nutritionally compromised [II].

2. Choice of specific pharmacologic treatment

Antidepressant medications that have been shown to be effective are listed in Table 1 [II]. The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Therefore, 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 individual patients, patient preference, quantity and quality of clinical trial data regarding the medication, and its cost (see Section V.A.1) [I]. On the basis of these considerations, the following medications are likely to be optimal for most patients: selective serotonin reuptake inhibitors (SSRIs), desipramine, nortriptyline, bupropion, and venlafaxine. In general, monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. Patients with major depressive disorder with atypical features are one group for whom several studies sug-

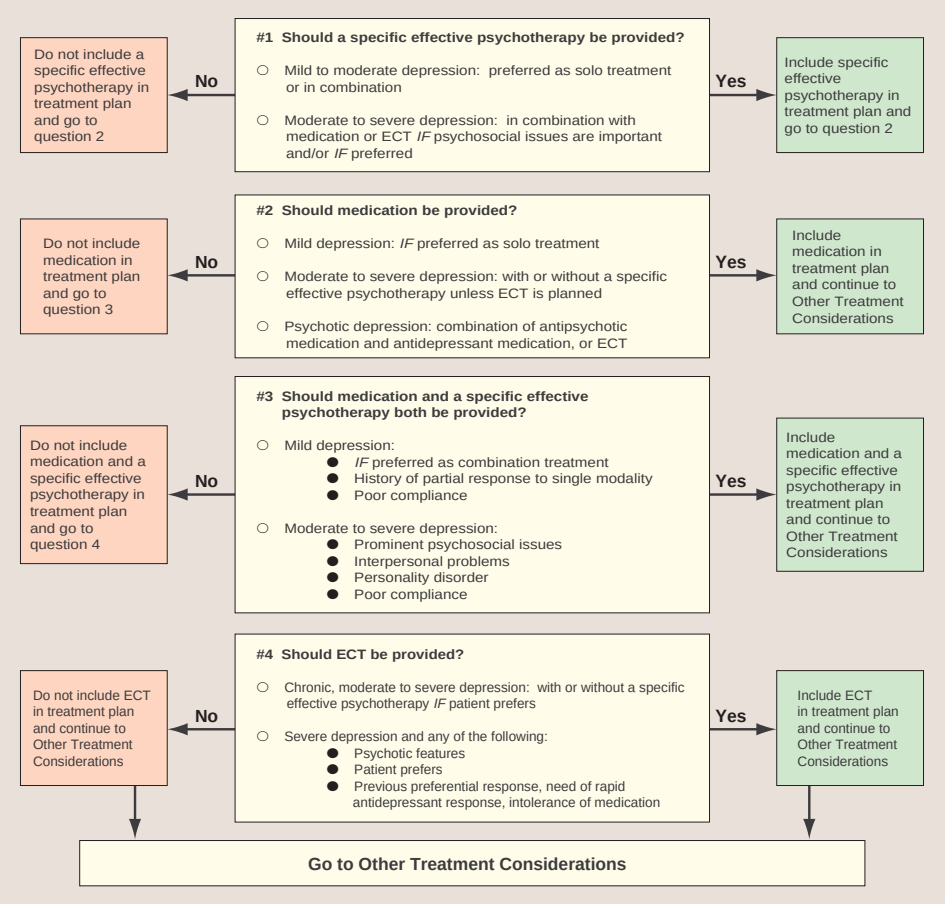


FIGURE 1. Choice of Treatment Modalities for Major Depressive Disorder.

gest MAOIs may be particularly effective; however, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile.

a) Implementation

When pharmacotherapy is part of the treatment plan, it must be integrated with the psychiatric management and any other treatments that are being provided (e.g., psychotherapy) [I]. Once an antidepressant medication has been selected, it can be started at the dose levels suggested in Table 1 [I]. Titration 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 comorbid illnesses. Patients who have started taking an antidepressant medication should be carefully monitored to assess their response to pharmacotherapy as well as the emergence of side effects, clinical condition, and safety [I] (see Figure 2). Factors to consider in determining the frequency of patient monitoring include the severity of illness, the patient's cooperation with treatment, the availability of social supports, and the presence of comorbid general medical problems. Visits should also be frequent enough to monitor and address suicidality and to promote treatment adherence. In practice, the frequency of monitoring during the acute phase of pharmacotherapy can vary from once a week in routine cases to multiple times per week in more complex cases.

TABLE 1. Commonly Used Antidepressant Medications (this list is representative, but not comprehensive)

Generic Name	Starting Dose (mg/day)[a]	Usual Dose (mg/day)
Tricyclics and tetracyclics		
Tertiary amine tricyclics		
Amitriptyline	25–50	100–300
Clomipramine	25	100–250
Doxepin	25–50	100–300
Imipramine	25–50	100–300
Trimipramine	25–50	100–300
Secondary amine tricyclics		
Desipramine[b]	25–50	100–300
Nortriptyline[b]	25	50–200
Protriptyline	10	15–60
Tetracyclics		
Amoxapine	50	100–400
Maprotiline	50	100–225
SSRIs[b]		
Citalopram	20	20–60[c]
Fluoxetine	20	20–60[c]
Fluvoxamine	50	50–300[c]
Paroxetine	20	20–60[c]
Sertraline	50	50–200[c]
Dopamine-norepinephrine reuptake inhibitors		
Bupropion[b]	150	300
Bupropion, sustained release[b]	150	300
Serotonin-norepinephrine reuptake inhibitors		
Venlafaxine[b]	37.5	75–225
Venlafaxine, extended release[b]	37.5	75–225
Serotonin modulators		
Nefazodone	50	150–300
Trazodone	50	75–300
Norepinephrine-serotonin modulator		
Mirtazapine	15	15–45
MAOIs		
Irreversible, nonselective		
Phenelzine	15	15–90
Tranylcypromine	10	30–60
Reversible MAOI-A		
Moclobemide	150	300–600
Selective noradrenaline reuptake inhibitor		
Reboxetine	—[d]	—[d]

[a]Lower starting doses are recommended for elderly patients and for patients with panic disorder, significant anxiety or hepatic disease, and general comorbidity.
[b]These medications are likely to be optimal medications in terms of the patient's acceptance of side effects, safety, and quantity and quality of clinical trial data.
[c]Dose varies with diagnosis; see text for specific guidelines.
[d]FDA approval is anticipated. When available, consult manufacturer's package insert or the Physician's Desk Reference for recommended starting and usual doses.

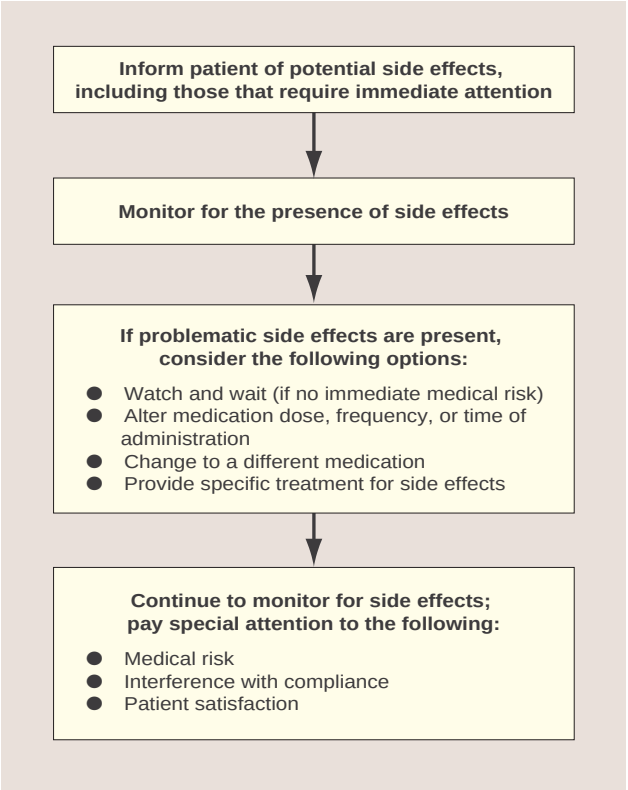


FIGURE 2. Management of Medication Side Effects.

b) Failure to respond

If at least moderate improvement is not observed following 6–8 weeks of pharmacotherapy, a reappraisal of the treatment regimen should be conducted [I]. Section II.B.2.b reviews options for adjusting the treatment regimen when necessary. 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 6–8 weeks of treatment, the psychiatrist should conduct another thorough review. An algorithm depicting the sequence of subsequent steps that can be taken for patients who fail to respond fully to treatment is provided in Figure 3.

3. Choice of specific psychotherapy

Cognitive behavioral therapy and interpersonal therapy are the psychotherapeutic approaches that have the best documented efficacy in the literature for the specific treatment of major depressive disorder, although rigorous studies evaluating the efficacy of psychodynamic psychotherapy have not been published [II]. When psychodynamic psychotherapy is used as a specific treatment, in addition to symptom relief, it is frequently associated with broader long-term goals. Patient preference and the availability of clinicians with appropriate training and expertise in the specific approach are also factors in the choice of a particular form of psychotherapy.

a) Implementation

When psychotherapy is part of the treatment plan, it must be integrated with the psychiatric management and any other treatments that are being provided (e.g., medication treatment) [I].

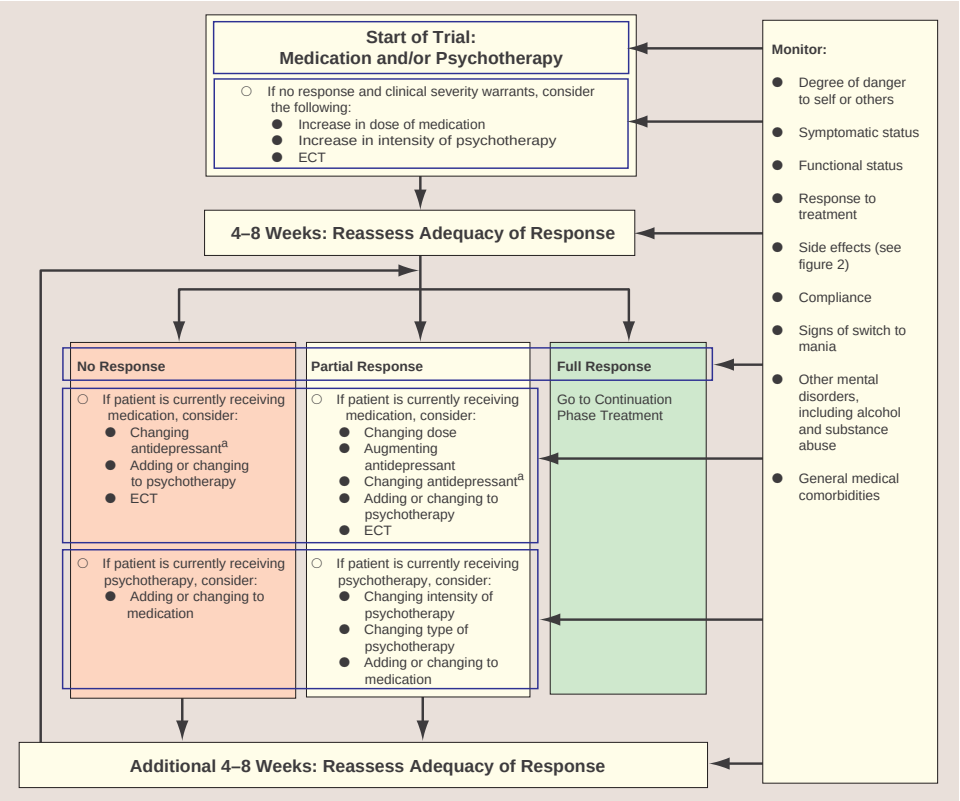


FIGURE 3. Acute Phase Treatment of Major Depressive Disorder.

[a]Choose either another antidepressant from the same class or, if two previous medication trials from the same class were ineffective, an antidepressant from a different class.

The optimal frequency of psychotherapy has not been rigorously studied in controlled trials. The psychiatrist should take into account multiple factors when determining the frequency for individual patients, including the specific type and goals of 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 suicidality. The frequency of outpatient visits during the acute phase generally varies from once a week in routine cases to as often as several times a week.

Regardless of the type of psychotherapy selected, the patient's response to treatment should be carefully monitored [I].

If more than one clinician is involved in providing the care, it is essential that all treating clinicians have sufficient ongoing contact with the patient and with each other to ensure that relevant information is available to guide treatment decisions [I].

b) Failure to respond

If after 4–8 weeks of treatment at least a moderate improvement is not observed, then a thorough review and reappraisal of the diagnosis, complicating conditions and issues, and treatment plan should be conducted [I]. Figure 3 and Section II.B.3.b review the options to consider.

TABLE 2. Considerations in the Decision to Use Maintenance Treatment

Factor	Component
Risk of recurrence	Number of prior episodes; presence of comorbid conditions; residual symptoms between episodes
Severity of episodes	Suicidality; psychotic features; severe functional impairments
Side effects experienced with continuous treatment	
Patient preferences	

4. Choice of medications plus psychotherapy

In general, the same issues that influence the specific choice of medication or psychotherapy when used alone should be considered when choosing treatments for patients receiving combined modalities [I].

5. Assessing the adequacy of response

It is not uncommon for patients to have a substantial but incomplete response in terms of symptom reduction or improvement in functioning during acute phase treatments. It is important not to conclude the acute phase of treatment for such patients, as a partial response is often associated with poor functional outcomes. When patients are found to have not fully responded to an acute phase treatment, a change in treatment should be considered as outlined in Figure 3 [II].

C. CONTINUATION PHASE

During the 16–20 weeks following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained on these agents to prevent relapse [I]. In general, the dose used in the acute phase is also used in the continuation phase. Although there has been less study of the use of psychotherapy in the continuation phase to prevent relapse, there is growing evidence to support the use of a specific effective psychotherapy during the continuation phase [I]. Use of ECT in the continuation phase has received little formal study but may be useful in patients for whom medication or psychotherapy has not been effective in maintaining stability during the continuation phase [II]. The frequency of visits must be determined by the patient's clinical condition as well as the specific treatments being provided.

D. MAINTENANCE PHASE

Following the continuation phase, maintenance phase treatment should be considered for patients to prevent recurrences of major depressive disorder [I]. Factors to consider are discussed in Table 2 and in Section II.D.

In general, the treatment that was effective in the acute and continuation phases should be used in the maintenance phase [II]. In general, the same full antidepressant medication doses are employed as were used in prior phases of treatment; use of lower doses of antidepressant medication in the maintenance phase has not been well studied. For cognitive behavioral therapy and interpersonal therapy, maintenance phase treatments usually involve a decreased frequency of visits (e.g., once a month).

TABLE 3. Risk Factors for Recurrence of Major Depressive Disorder

- Prior history of multiple episodes of major depressive disorder
- Persistence of dysthymic symptoms after recovery from an episode of major depressive disorder
- Presence of an additional nonaffective psychiatric diagnosis
- Presence of a chronic general medical disorder

The frequency of visits in the maintenance phase must be determined by the patient's clinical condition as well as the specific treatments being provided. The frequency required could range from as low as once every 2–3 months for stable patients who require only psychiatric management and medication monitoring to as high as multiple times a week for those in whom psychodynamic psychotherapy is being conducted.

E. DISCONTINUATION OF ACTIVE TREATMENT

The decision to discontinue active treatment should be based on the same factors considered in the decision to initiate maintenance treatment, including the probability of recurrence, the frequency and severity of past episodes, the persistence of dysthymic symptoms after recovery, the presence of comorbid disorders, and patient preferences [I]. In addition to the factors listed in Table 2 and Table 3, patients and their psychiatrists should consider patient response, in terms of both beneficial and adverse effects, to maintenance treatments.

Specific clinical features that will influence the general treatment are discussed in Section III.

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

The following discussion regarding formulation and implementation of a treatment plan refers specifically to patients with major depressive disorder. For the treatment of patients found to have depressive symptoms within the context of bipolar disorder, readers should refer to the *Practice Guideline for the Treatment of Patients With Bipolar Disorder* (2). The treatment recommendations that follow may have some relevance for patients who have depressive symptoms on the basis of other syndromes, such as dysthymia, although this cannot be fully established with the existing scientific literature.

The successful treatment of patients with major depressive disorders is promoted by an initial thorough assessment of the patient. Treatment then consists of an acute phase lasting a minimum of 6–8 weeks, during which remission is induced. Remission is defined as a return to the patient's baseline level of symptom severity and functioning and should not be confused with substantial but incomplete improvement. After achieving remission, the patient enters the continuation phase, which usually lasts 16–20 weeks, during which time the remission is preserved and relapse is prevented. Relapse is generally defined as the reemergence of significant depressive symptoms or dysfunction following a remission. Patients who successfully complete the continuation phase without relapse then enter the maintenance phase of treatment. The goal during the maintenance phase is to protect susceptible patients against recurrence of subsequent major depressive episodes; the duration of the maintenance phase will vary depending on the frequency and severity of prior major depressive episodes.

Psychiatrists initiating treatment of an episode of major depressive disorder have at their disposal a number of medications, a variety of psychotherapeutic approaches, ECT, and other treatment modalities (e.g., light therapy). These various interventions may be used alone or in combination. The psychiatrist must determine the setting that will most likely ensure the patient's safety as well as promote improvement in the patient's condition.

A. PSYCHIATRIC MANAGEMENT

Psychiatric management consists of a broad array of interventions and activities that should be instituted by psychiatrists for all patients with major depressive disorder. The specific components of psychiatric management that must be addressed for all patients are described in more detail below.

1. Perform a diagnostic evaluation

Patients with major depressive disorder symptoms should receive a thorough diagnostic evaluation both to determine whether a diagnosis of depression is warranted and to reveal the presence of other psychiatric or general medical conditions. The general principles and components of a complete psychiatric evaluation have been outlined in the American Psychiatric Association's *Practice Guideline for Psychiatric Evaluation of Adults* (3). These should include a history of the present illness and current symptoms; a psychiatric history, including symptoms of mania as well as a treatment history that particularly notes current treatments and responses to previous treatments; a general medical history and history of substance use disorders; a personal history (e.g., psychological development, response to life transitions, and major life events); a social, occupational, and family history; a review of the patient's medications; a review of systems; a mental status examination; a physical examination; and diagnostic tests as indicated.

2. Evaluate the safety of patient and others

A careful assessment of the patient's risk for suicide is crucial. Some components of an evaluation for suicide risk are summarized in Table 4. An assessment of the presence of suicidal ideation is essential, including the degree to which the patient intends to act on any suicidal ideation and the extent to which the patient has made plans for or begun to prepare for suicide. The availability of means for suicide should be inquired about and a judgment made concerning the lethality of those means. Clinical factors that may increase the likelihood of a patient acting on suicidal ideation should be assessed, including the presence of psychotic symptoms, severe anxiety, panic attacks, and alcohol or substance use. Whether a patient has a history of making suicide attempts and the nature of those attempts should be evaluated. Patients should also be asked about suicide in their family history and recent exposure to suicide or suicide attempts by others. A complete assessment of suicide risk should be individualized to the particular circumstances of the patient and include an evaluation of the patient's strengths and motivation to seek help. Patients who are found to possess suicidal or homicidal ideation, intention, or plans require close monitoring. Measures such as hospitalization (involuntary when indicated) should be considered for those at significant risk. However, it should be kept in mind that the ability to predict suicide attempts and completed suicide is poor, with both many false positives (i.e., patients who appear more likely to make attempts or complete suicide but who do not) and false negatives (i.e., patients who appear less likely to make attempts or complete suicide but who do). For this reason, despite the best efforts of the psychiatrist, some patients may engage in self-harm or harm toward others.

TABLE 4. Components of an Evaluation for Suicide Risk

- Presence of suicidal or homicidal ideation, intent, or plans
- Access to means for suicide and the lethality of those means
- Presence of psychotic symptoms, command hallucinations, or severe anxiety
- Presence of alcohol or substance use
- History and seriousness of previous attempts
- Family history of or recent exposure to suicide

3. Evaluate functional impairments

Major depressive disorder is frequently associated with functional impairments, and the presence, type(s), and severity of dysfunction should be evaluated. Impairments can include deficits in interpersonal relationships, work, living conditions, and other medical or health-related needs. Identified impairments in functioning should be addressed; for example, some patients may require assistance in scheduling absences from work or other responsibilities, whereas others may require encouragement to not make any major life changes while in a major depressive disorder state. Patients should also be encouraged to set realistic, attainable goals for themselves in terms of desirable levels of functioning.

4. Determine a treatment setting

Treatment settings for patients with major depressive disorder include a continuum of possible levels of care, from involuntary hospitalizations to day programs to ambulatory settings. In general, patients should be treated in the 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, comorbidity, suicidality, homicidality, level of functioning, and available support system. The determination of a treatment setting should also include consideration of patients' ability to adequately care for themselves, provide reliable feedback to the psychiatrist, and cooperate with treatment of their major depressive disorder.

Patients who exhibit suicidal or homicidal ideation, intention, or a plan require close monitoring. Hospitalization is usually indicated for patients who are considered to pose a serious threat of harm to themselves or others. If patients refuse, they can be hospitalized involuntarily if their condition meets criteria for involuntary admission of the local jurisdiction. Severely ill patients who lack adequate social support outside of a hospital setting should be considered for admission to a hospital or intensive day program. Additionally, those 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 ability to benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment.

5. Establish and maintain a therapeutic alliance

Regardless of the treatment modalities ultimately selected for patients, it is important for the psychiatrist to establish a therapeutic alliance with the patient. Major depressive disorder is often a chronic condition that requires patients to actively participate and adhere to treatment plans for long periods. Unfortunately, features of major depressive disorder may include poor motivation, pessimism over the effectiveness of treatments, decrements in cognition such as attention or memory, decreased self-care, and possibly intentional self-harm. In addition, successful treatment may require patients to tolerate side effects. For these reasons, a strong treatment alliance between patient and psychiatrist is crucial. To establish and maintain a therapeutic alliance with patients, it is important for psychiatrists to pay attention to the concerns of patients

and their families as well as their wishes for treatment. Management of the therapeutic alliance should include awareness of transference and countertransference issues, even if these are not directly addressed in treatment.

6. Monitor the patient's psychiatric status and safety

As treatment progresses, different features and symptoms of the patient's illness may emerge or subside. Monitoring the patient's status for the emergence of 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. The psychiatrist should be vigilant to changes in the patient's psychiatric status, including major depressive disorder symptoms as well as symptoms of other potential comorbid conditions. Significant changes in a patient's psychiatric status or the emergence of new symptoms may warrant a diagnostic reevaluation of the patient.

7. Provide education to the patient and, when appropriate, to the family

Education concerning major depressive disorder and its treatments should be provided to all patients. When appropriate, education should also be provided to involved family members. Specific educational elements may be especially helpful in some circumstances; for example, emphasizing that major depressive disorder is a real illness and that effective treatments are both necessary and available may be crucial 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.

8. Enhance treatment adherence

The successful treatment of major depressive disorder requires close adherence to treatment plans, in some cases for long or indefinite durations. Especially while symptomatic, patients with major depressive disorder may be poorly motivated, unduly pessimistic over their chances of recovery with treatment, suffering from deficits in memory, or taking less care of themselves. In addition, the side effects or requirements of treatments may lead to nonadherence. Particularly during the maintenance phase, euthymic patients may tend to undervalue the benefits of treatment and focus on the burdens of treatment. Psychiatrists should recognize these possibilities, encourage the patient to articulate any concerns regarding adherence, and emphasize the importance of adherence for successful treatment. Specific components of a message to patients that have been shown to improve adherence include emphasizing: 1) when and how often to take the medicine; 2) the need for at least 2–4 weeks before beneficial effects may be noticed; 3) the need to take medication even after feeling better; 4) the need to consult with the doctor before discontinuing medication; and 5) what to do if problems or questions arise (4). Some patients, particularly elderly patients, have been shown to have improved adherence when both the complexity of medication regimens and the costs of treatments are minimized. Severe or persistent problems of nonadherence may represent psychological conflicts or psychopathology for which psychotherapy should be considered. When family members are involved, they can also be encouraged to play a helpful role in improving adherence.

9. Work with the patient to address early signs of relapse

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. 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.

B. ACUTE PHASE

1. Choice of initial treatment modality

In the acute phase, in addition to psychiatric management, the psychiatrist may choose between several initial treatment modalities, including pharmacotherapy, psychotherapy, the combination of medications and psychotherapy, or ECT. A discussion of the potential role of other treatments (e.g., light therapy and St. John's wort) can be found in Section V. Selection of an initial treatment modality should be influenced by both clinical (e.g., severity of symptoms) and other factors (e.g., patient preference) (Figure 1).

a) Antidepressant medications

When pharmacotherapy is part of the treatment plan, it must be integrated with the psychiatric management and any other treatments that are being provided (e.g., psychotherapy). 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 history of prior positive response to antidepressant medications, severity of symptoms, significant sleep and appetite disturbances or agitation, or anticipation of the need for maintenance therapy. Other issues that may be important considerations in the decision to use antidepressant medication include patient preference or the lack of available adequate alternative treatment modalities. Patients with major depressive disorder with psychotic features require either the combined use of antidepressant and antipsychotic medications or ECT.

b) Psychotherapy

A specific, effective psychotherapy alone may be considered as an initial treatment modality for patients with mild to moderate major depressive disorder. Clinical features that may suggest the use of a specific psychotherapy include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, or axis II comorbidity. Patient preference for psychotherapeutic approaches is an important factor that should be considered in the decision to use psychotherapy as the initial treatment modality. Pregnancy, lactation, or the wish to become pregnant may also be an indication for psychotherapy as an initial treatment.

c) Psychotherapy plus antidepressant medications

The combination of a specific effective psychotherapy and medication may be a useful initial treatment choice for patients with psychosocial issues, intrapsychic conflict, interpersonal problems, or a comorbid axis II disorder together with moderate to severe major depressive 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 treatments may also warrant combined treatment with pharmacotherapy and psychotherapeutic approaches that focus on treatment adherence.

d) Electroconvulsive therapy

ECT should be considered for patients with major depressive disorder with a high degree of symptom severity and functional impairment as well as in cases in which psychotic symptoms or catatonia are present. ECT may also be the treatment modality of choice for patients in whom there is an urgent need for response, such as patients who are suicidal or who are refusing food and are nutritionally compromised. The presence of comorbid general medical conditions that preclude the use of antidepressant medications, a prior history of positive response to ECT, and patient preference are other important considerations that may influence the psychiatrist's decision to select ECT as a treatment modality.

TABLE 5. Factors to Consider in Choosing a First-Line Antidepressant Medication

- Anticipated side effects and their safety or tolerability
- History of prior response in patient or family member
- Patient preference
- Cost
- Quantity and quality of clinical trial data
- MAOIs: generally reserve for patients who do not respond to other treatments
- SSRIs or MAOIs: consider for patients with atypical symptoms

2. Choice of specific pharmacologic treatment

Antidepressant medications that have been shown to be effective are listed in Table 1. The effectiveness of antidepressant medications is generally comparable between classes and within classes of medications. Therefore, 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 individual patients, patient preference, quantity and quality of clinical trial data regarding the medication, and its cost (Table 5). On the basis of these considerations, the following medications are likely to be optimal agents for most patients: SSRIs, desipramine, nortriptyline, bupropion, and venlafaxine. Additional considerations that may influence the choice of antidepressant medication include a history of prior response to a medication and the presence of comorbid psychiatric or general medical conditions. For example, secondary amine tricyclic antidepressant medications may not be optimal in patients with cardiovascular conditions, cardiac conduction defects, closed-angle glaucoma, urinary retention, or significant prostatic hypertrophy. SSRIs can carry a risk of sexual side effects and may be more expensive because of the lack of currently available generic preparations. Similarly, the specific side effect profiles and higher costs should be considerations in decisions regarding use of other newer antidepressant medications. In general, MAOIs should be restricted to patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. Patients with major depressive disorder with atypical features are one group for whom several studies suggest MAOIs may be particularly effective; however, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile.

a) Implementation of pharmacotherapy

Once an antidepressant medication has been selected it can be started at doses suggested in Table 1. 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 comorbid conditions. In elderly or medically frail patients, the starting and therapeutic doses should be reduced, generally to half of the usual adult doses.

Patients who have started taking an antidepressant medication should be carefully monitored to assess the response to pharmacotherapy as well as the emergence of side effects, clinical condition, and safety (see Figure 2). There are limited clinical trial data to guide the decision regarding the frequency of monitoring patients during pharmacotherapy. Factors to consider when determining this frequency include the severity of illness, the patient's cooperation with treatment, the availability of social supports, and the presence of comorbid general medical problems. Visits should also be frequent enough to monitor and address suicidality and to promote treatment adherence. Experienced researchers have found that patients in clinical trials appear to benefit from monitoring once a week or more to enhance adherence rates and to avoid the demoralization that may occur before the onset of beneficial effects. In clinical practice, the frequency of monitoring during the acute phase of pharmacotherapy may vary from once a week in routine cases to multiple times per week in more complex cases. The method of monitoring may vary depending upon the clinical context (e.g., face-to-face visits, telephone contact, or contact with another clinician knowledgeable about the patient and the treatment modality).

TABLE 6. Required Washout Times Between Antidepressant Trials

Antidepressant Change	Minimum Washout Period
To MAOI from drug with long-half-life metabolites (e.g., fluoxetine)	5 weeks
To MAOI from drug without long-half-life metabolites (e.g., tricyclic antidepressant, paroxetine, fluvoxamine, venlafaxine) or other MAOI	2 weeks
To non-MAOI antidepressant from MAOI	2 weeks

Improvement with pharmacotherapy can be observed after 4–8 weeks of treatment. If at least a moderate improvement is not observed in this time period, reappraisal and adjustment of the pharmacotherapy should be considered.

b) Failure to respond

If at least moderate improvement is not observed following 4–8 weeks of pharmacotherapy, a reappraisal of the treatment regimen should be conducted. An algorithm depicting the sequence of subsequent steps that can be taken and possible outcomes for patients who do not respond fully to treatment is provided in Figure 3. It is important to keep in mind when employing such algorithms that they are based largely on clinical experience and only limited clinical trial data.

First, patient adherence and pharmacokinetic/pharmacodynamic factors affecting treatment should be investigated, in some cases through determination of serum antidepressant medication levels. Following this review, the treatment plan can be revised by implementing one of several therapeutic options, including maximizing the initial medication treatment, switching to another non-MAOI antidepressant medication (Table 1 and Table 6), augmenting antidepressant medications with other agents or psychotherapy, using an MAOI, or ECT (5).

Maximizing the initial treatment regimen is perhaps the most conservative strategy. For patients who have shown a partial response, particularly those with features of personality disorders, extending the antidepressant medication trial (e.g., by 2–4 weeks) may allow some patients to respond more fully (6). Use of higher antidepressant doses may be helpful for patients who have received only modest doses or for those who for pharmacodynamic reasons have low serum drug levels despite usual doses and adherence. Patients who have had their dose increased should be monitored for an increase in the severity of side effects.

Switching to a different non-MAOI antidepressant medication is a common strategy for treatment-refractory patients, especially those who have not shown at least partial response to the initial medication regimen. Patients can be switched to a non-MAOI antidepressant medication from the same pharmacologic class (e.g., from an SSRI to another SSRI) or to one from a different pharmacologic class (e.g., from an SSRI to a tricyclic antidepressant) (see Table 1 and Table 6) (5).

Augmentation of non-MAOI antidepressant medications may be helpful, particularly for patients who have had a partial response to antidepressant monotherapy. Options include adding a second non-MAOI antidepressant medication from a different pharmacologic class, taking care to avoid drug-drug interactions, or adding another adjunctive medication such as lithium, thyroid hormone, an anticonvulsant, or psychostimulants.

Adding, changing, or increasing the intensity of psychotherapy should be considered for patients with major depressive disorder who do not respond to medication treatment. Additional strategies for patients who do not respond adequately to treatment include switching to an MAOI after allowing sufficient time between medications to avoid hazardous interactions. ECT also remains perhaps the most effective therapy for treatment-resistant patients.

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 comorbid general medical conditions or psychiatric conditions (e.g., alcohol or substance abuse); and uncovering and addressing psychosocial issues that may be impeding recovery. If no new information is uncovered to explain the patient's lack of adequate response, other treatment options should be considered, including obtaining a consultation and possibly ECT.

3. Choice of a specific psychotherapy

Cognitive behavioral therapy and interpersonal therapy have the best-documented effectiveness in the literature for the specific treatment of major depressive disorder. When psychodynamic psychotherapy is used as a specific treatment, in addition to symptom relief, it is frequently associated with broader long-term goals. Patient preference and the availability of clinicians with appropriate training and expertise in specific psychotherapeutic approaches are also factors in the choice of a particular form of psychotherapy. Other clinical factors influencing the type of psychotherapy employed are the stage and severity of the major depressive disorder episode. For example, although some data suggest that cognitive behavioral therapy alone may be effective for patients with moderate to severe major depressive disorder, most such patients will require medication. In general, the choice among psychotherapeutic approaches is dependent on patient preference, with particular regard to whether the goals are mainly symptomatic improvement versus broader psychosocial goals.

During the initial phases of treatment for patients with moderate to severe major depressive disorder, psychiatric management will have to include support and psychoeducation for the patient and the family, permission for the patient to excuse himself or herself from duties impossible to perform, and assistance regarding the making or postponing of major personal and business decisions. Some patients at this stage may not have the emotional energy or cognitive ability required for insight-oriented psychotherapy. If indicated, this may be initiated later in the course of recovery.

a) Implementation

When psychotherapy is part of the treatment plan, it must be integrated with the psychiatric management and any other treatments that are being provided (e.g., medication treatment). The optimal frequency of psychotherapy has not been rigorously studied in controlled trials. The psychiatrist should take into account 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 suicidality. Also affecting the frequency of psychotherapy visits are the severity of illness, the patient's cooperation with treatment, the availability of social supports, cost, geographic accessibility, and presence of comorbid general medical problems. The frequency of outpatient visits during the acute phase generally varies from once a week in routine cases to as often as several times a week. Transference-focused treatments tend to require more frequent and regular visits.

Regardless of the type of psychotherapy selected, the patient's response to treatment should be carefully monitored. If after 4–8 weeks of treatment at least a moderate improvement is not observed, then a thorough review and reappraisal of the treatment plan should be conducted.

There are no definitive studies to determine when it is preferable to have the psychiatrist provide all treatments (sometimes referred to as the "integrated" model) versus when it might be preferable to have a different clinician provide the psychotherapy, with the psychiatrist providing the psychiatric management and the medication (sometimes referred to as "split" treat-

ment). The expertise of the psychiatrist in providing the desired type of psychotherapy and the preferences of the patient are frequently factors in the decision. The integrated treatment model provides for better coordination of care. Lower costs have been used as a rationale in support of the split-treatment model. However, it is not clear that the costs of that model are actually lower than for the integrated model (7).

If the split model is used, it is essential that the psychiatrist who is providing the psychiatric management and the medication treatment meets with the patient frequently enough to monitor his or her care. It is also essential that the two (or more) treating clinicians have sufficient ongoing contact to ensure that relevant information is available to guide treatment decisions.

b) Failure to respond

The patient's condition and response to therapeutic interventions should be carefully monitored from the outset of psychotherapy. If the patient's condition fails to stabilize or is deteriorating, reassessment is indicated (8). If after 4–8 weeks of treatment at least a moderate improvement is not observed, then a thorough review and reappraisal of the diagnosis, complicating conditions and issues, and treatment plan should be conducted. In many cases, the treatment plan can be revised by the addition or substitution of pharmacotherapy (see Figure 3). Following any revision or refinement of treatment, the patient should continue to be closely monitored. If there continues to not be at least a moderate improvement in major depressive disorder symptoms after an additional 4–8 weeks of treatment, another thorough review, reappraisal, and revision of the treatment plan should be conducted.

4. Choice of medications plus psychotherapy

There are relatively few empirical data from clinical trials to help guide the selection of particular antidepressant medications and 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 those employed for patients receiving them as a monotherapy.

Patients receiving combined antidepressant medication and psychotherapy should also be monitored closely for treatment effect, side effects, clinical condition, and safety. If after 4–8 weeks there is not at least a moderate improvement, a thorough review should be conducted, including of the patient's adherence and pharmacokinetic/pharmacodynamic factors affecting treatment. The treatment plan can be revised by using many of the same therapeutic options described for patients who have not responded to treatment with either modality alone. Following any change in treatment, the patient should continue to be monitored, and if there is not at least a moderate improvement in major depressive disorder symptoms after an additional 4–8 weeks of treatment, another thorough review should be conducted. Other treatment options should be considered, including clinical consultation or possibly ECT.

5. Assessing the adequacy of treatment response

The goal of acute phase treatment for major depressive disorder is to return patients to their baseline levels of symptomatic and functional status. However, it is not uncommon for patients to have a substantial but incomplete response in terms of symptom reduction or improvement in functioning during acute phase treatment. It is important not to conclude the acute phase of treatment for such patients, as a partial response is often associated with poor functional outcomes.

Identifying patients who have not had a complete response to treatment and formally assessing the extent to which patients have returned to their baseline may be aided by the use of structured measures of depression symptom severity and functional status. When patients are found to have not fully responded to an acute phase treatment, a change in treatment should be considered, as outlined in Figure 3.

C. CONTINUATION PHASE

During the 16–20 weeks following remission, patients who have been treated with antidepressant medications in the acute phase should be maintained with these agents to prevent relapse. In general, the dose used in the acute phase is also used in the continuation phase. Some psychiatrists combine a decrease in the dose with careful monitoring in the continuation phase; however, there are no data to support the effectiveness of this approach. Although there has been less study of the use of psychotherapy in the continuation phase to prevent relapse, there is growing evidence to support the use of a specific effective psychotherapy during the continuation phase. Use of ECT in the continuation phase has received little formal study. The frequency of visits must be determined by the patient's clinical condition as well as the specific treatments being provided.

During the continuation phase, the frequency of visits may vary. For stable patients in whom the visits are for the purpose of providing psychiatric management, the frequency could be once every 2–3 months. For other patients, such as those in whom active psychotherapy is being conducted, the frequency required may be as high as multiple times a week. If maintenance phase treatment is not indicated for patients who remain stable following the continuation phase, patients may be considered for discontinuation of treatment. If treatment is discontinued, patients should be carefully monitored for relapse, and treatment should be promptly reinstituted if relapse occurs.

D. MAINTENANCE PHASE

On average, 50%–85% of patients with a single episode of major depressive disorder will have at least one more episode. Therefore, following the continuation phase, maintenance phase treatment should be considered for patients to prevent recurrences of major depressive episodes. Factors that should be considered when deciding whether to use maintenance treatment are summarized in Table 2.

In general, the treatment that was effective in the acute and continuation phases should be used in the maintenance phase. In general, the same full antidepressant medication doses are employed as were used in prior phases of treatment; use of lower doses of antidepressant medication in the maintenance phase has not been well studied. For cognitive behavioral therapy and interpersonal therapy, maintenance phase treatments usually involve a decrease in frequency of visits (e.g., once a month). Psychodynamic psychotherapy usually continues at the same frequency in the effort to explore the role of axis II disorders or other psychological factors in predisposing to depressive episodes.

Although the effectiveness of combinations of antidepressant medication and psychotherapy in the maintenance phase has not been well studied, such combinations may be an option for some patients. Patients who exhibit repeated episodes of moderate or severe major depressive disorder despite optimal pharmacologic treatment or patients who are medically ineligible for such treatment may be maintained with periodic ECT. There has been little formal study of other treatment modalities in the maintenance phase.

Similar to the continuation phase, the frequency of visits may vary in the maintenance phase. The frequency required could 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 in whom psychodynamic psychotherapy is being conducted. Maintenance ECT is usually administered monthly; individuals for whom this is insufficient may find treatment at more frequent intervals to be beneficial. The optimal length of maintenance treatment is not known and may also vary depending on the frequency and severity of recurrences, tolerability of treatments, and patient preferences. For some patients, maintenance treatment may be required indefinitely.

E. DISCONTINUATION OF ACTIVE TREATMENT

The precise timing and method of discontinuing psychotherapy and pharmacotherapy for depression have not been systematically studied. The decision to discontinue maintenance treatment should be based on the same factors considered in the decision to initiate maintenance treatment, including the probability of recurrence, the frequency and severity of past episodes, the persistence of depressive symptoms after recovery, the presence of comorbid disorders, and patient preferences. In addition to the factors listed in Table 2 and Table 3, patients and their psychiatrists should consider patient response, in terms of both beneficial and adverse effects, to maintenance treatments.

When the decision is made to discontinue or terminate psychotherapy in the maintenance phase, the manner in which this is done should be individualized to the patient's needs and will depend on the type of psychotherapy, duration, and intensity of treatment. For example, maintenance treatment with cognitive behavioral therapy may have been of a preplanned length and not require extensive time for termination; on the other hand, a long-term psychodynamic psychotherapy may require greater time for and attention to the termination process.

When the decision is made to discontinue maintenance pharmacotherapy, it is best to taper the medication over the course of at least several weeks. Such tapering may allow for the detection of emerging symptoms or recurrences when patients are still partially treated and therefore more easily returned to full therapeutic intensity. In addition, such tapering can help minimize the risks of antidepressant medication discontinuation syndromes (9). Discontinuation syndromes are problematic because their symptoms include disturbances of mood, energy, sleep, and appetite and can be mistaken for or mask signs of relapse (10). 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 be given even longer, more gradual tapering (11).

After the discontinuation of active treatment, patients should be reminded of the potential for a depressive relapse. Early signs of major depressive disorder should be reviewed, and a plan for seeking treatment in the event of recurrence of symptoms should be established. Patients should continue to be monitored over the next several months to identify those in whom a relapse has occurred. If a patient suffers a relapse upon discontinuation of medication, treatment should be promptly reinitiated. In general, the previous treatment regimen to which the patient responded in the acute and continuation phases should be considered. Patients who relapse following discontinuation of antidepressant medication therapy should be considered to have suffered from another major depressive disorder episode and should receive another round of adequate acute phase treatment followed by continuation phase treatment and possibly maintenance phase treatment.

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

A. PSYCHIATRIC FEATURES

1. Suicide risk

Patients with major depressive disorder are at greater risk for suicide. Suicide risk should be assessed initially and over the course of treatment. If the patient has suicidal ideation, intention, or a plan, close surveillance is necessary. Factors to be considered 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, and

past history of suicidal behavior. The risk of suicide in some patients recovering from major depressive disorder increases transiently as they develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness. Clinicians must be aware of the risk of suicide throughout the course of treatment. However, the prediction of suicide attempts or suicide completion for any given patient is extremely difficult, with both many false positives (patients who appear to be at greater risk of making attempts or completing suicide but who do not) and false negatives (patients who appear to be at decreased risk but who ultimately do make attempts or complete suicide). Therefore, even with the best possible care, a small proportion of patients with major depressive disorder are likely to die by suicide.

2. Psychotic features

Major depressive disorder with psychotic features carries a higher risk of suicide than does major depressive disorder uncomplicated by psychosis (12), and it constitutes a risk factor for recurrent major depressive disorder. Major depressive disorder with psychotic features responds better to treatment with a combination of an antipsychotic medication and an antidepressant medication than to treatment with either component alone (13). Lithium augmentation is helpful in some patients who have not responded to combined antidepressant-antipsychotic medication treatment (14). ECT is highly effective in major depressive disorder with psychotic features and may be considered a first-line treatment for this disorder (15).

3. Catatonic features

Catatonic features may occur in the context of mood disorders and are characterized by at least two of the following manifestations: motoric 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 (16). Catatonia often dominates the presentation and may be so severe as to be life-threatening, compelling the consideration of urgent biological treatment. Immediate relief may often be obtained by the intravenous administration of benzodiazepines such as lorazepam or amobarbital. For patients who show some relief, continued oral administration of lorazepam, diazepam, or amobarbital may be helpful. Concurrent antidepressant medication treatments should be considered. When relief is not immediately obtained by administering barbiturates or benzodiazepines, the urgent provision of ECT should be considered. The efficacy of ECT, usually apparent after a few treatments, is well documented; ECT may initially be administered daily. After the catatonic manifestations are relieved, treatment may be continued with antidepressant medications, lithium, antipsychotics, or a combination of these compounds, as determined by the patient's condition.

4. Atypical features

Atypical major depressive disorder features include vegetative symptoms of reversed polarity (i.e., increased rather than decreased sleep, appetite, and weight), marked mood reactivity, sensitivity to emotional rejection, phobic symptoms, and a sense of severe fatigue that creates a sensation of leaden paralysis or extreme heaviness of the arms or legs (17). Patients need not have all of these features to be diagnosed as having atypical major depressive disorder (18). There is some overlap between patients with atypical major depressive disorder and patients with anergic bipolar major depressive disorder. Although tricyclic antidepressant medications yield response rates of only 35%–50% in patients with atypical major depressive disorder, several other antidepressant classes have been found to be more effective, yielding response rates of 55%–75% (comparable to the response rate of typical forms of major depressive disorder to tricyclic therapy) (19, 20). Results of several studies suggest that SSRIs, MAOIs, and possibly bupropion may be more effective treatments for atypical major depressive disorder (21–23). The presence and severity of specific symptoms as well as safety considerations should help

guide the choice of treatment for atypical major depressive disorder. For example, if a patient does not wish to, cannot, or is unlikely to adhere to the dietary and medication precautions associated with MAOI treatment, the use of an alternative antidepressant medication is indicated; on the other hand, bupropion may be anxiogenic and not preferred in cases where anxiety predominates.

5. Alcohol or substance abuse or dependence

Because of the frequent comorbidity of major depressive disorder and alcohol or other substance abuse, the psychiatrist should make every effort to obtain a detailed history of the patient's substance use. If there is suspicion that there is a problem in this area, the clinician should consider questioning a collateral for confirmation. If the patient is found to have a substance use disorder, a program to secure abstinence should be regarded as a principal priority in the treatment. A patient suffering from major depressive disorder with comorbid addiction is more likely to require hospitalization, more likely to attempt suicide, and less likely to comply with treatment than is a patient with major depressive disorder of similar severity not complicated by this factor. Some alcohol- and chemical-abusing patients reduce their consumption of these substances upon remediation of an underlying major depressive disorder, making the recognition and treatment of major depressive disorder doubly important for such individuals.

It is advisable, if other factors permit, to detoxify patients before initiating antidepressant medication therapy. Identifying the patients who should be started on a regimen of antidepressant medication therapy earlier, after initiation of abstinence, is difficult. A positive 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 would benefit from antidepressant medication treatment, which may then be started earlier in treatment.

Concurrent drug abuse, especially with stimulant drugs, predisposes the patient to toxic interactions with MAOIs, although there have been few reports of such events (24). Benzodiazepines and other sedative-hypnotics carry the potential for abuse or dependence and should be used cautiously except as part of a detoxification regimen. Benzodiazepines have also been reported to contribute to major depressive disorder symptoms. 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 (if available), therapeutic effects, and side effects to avoid either psychotropic medication intoxication or inadequate treatment.

6. Comorbid panic or other anxiety disorder

Panic disorder complicates major depressive disorder in 15%–30% of the cases (25). Individuals with symptoms of both disorders manifest greater degrees of impairment than do patients with major depressive disorder only. In major depressive disorder with comorbid anxiety or panic disorder, both the major depressive disorder symptoms and anxiety symptoms have been shown to respond to antidepressant medication treatment (26). Although there is some evidence that MAOIs may be more effective than other classes for patients with major depressive disorder and anxiety symptoms (25), therapy should first be initiated with a non-MAOI agent because of the somewhat greater complications associated with MAOIs. Tricyclic antidepressant medications and SSRIs may initially worsen rather than alleviate anxiety and panic symptoms; these medications should therefore be introduced at a low dose and slowly increased when used to treat such patients. Bupropion has been reported as ineffective in the treatment of panic disorder (27). Alprazolam may sometimes be used with benefit in conjunction with antidepressant medications; in general, benzodiazepines should not be used as the primary pharmacologic agent for patients with major depressive disorder and anxiety symptoms, especially patients with more severe forms of major depressive disorder.

Obsessive-compulsive symptoms are also more common in patients with major depressive disorder episodes. Clomipramine and the SSRIs have demonstrated efficacy in the management of obsessive-compulsive symptoms in addition to also being effective antidepressant medications (28, 29). Such agents may be used to good effect when obsessive symptoms accompany an episode of major depressive disorder.

7. Major depressive disorder–related cognitive dysfunction (pseudodementia)

Major depressive disorder is routinely accompanied by signs and symptoms of cognitive inefficiency. Some patients have both major depressive disorder and dementia, while others have major depressive disorder that causes cognitive impairment (i.e., pseudodementia). In the latter case, the treatment of the major depressive disorder should reverse the signs and symptoms of cognitive dysfunction. Many patients complain that their thoughts are slowed and their capacity to process information is reduced; they also display diminished attention to their self-care and to their environment. Transient cognitive impairments, especially involving attention, concentration, and memory storage and retrieval, are demonstrable through neuropsychological testing (30). In extreme examples, especially in the elderly, these complaints and deficits are so prominent that patients may appear demented. Major depressive disorder–related cognitive dysfunction is a reversible condition that resolves with treatment of the underlying major depressive disorder. Several clinical features help differentiate major depressive disorder pseudodementia from true dementia. When performing cognitive tasks, pseudodemented patients generally exert relatively less effort but report more incapacity than do demented patients. The latter group, especially in more advanced stages, typically neither recognize nor complain of their cognitive failures, since insight is impaired; in comparison, pseudodemented patients characteristically complain bitterly that they cannot think or cannot remember. Major depressive disorder pseudodementia lacks the signs of cortical dysfunction (i.e., aphasia, apraxia, agnosia) encountered in degenerative dementia, such as Alzheimer's disease (31). It is vital that individuals with major depressive disorder–related cognitive disturbance not be misdiagnosed and thereby denied vigorous antidepressant medication treatment or ECT.

8. Dysthymia

Antidepressant medications have been found to be effective in the treatment of dysthymia and chronic major depressive disorder, including tricyclic antidepressants, SSRIs, other newer agents, and MAOIs; unfortunately, there is little evidence from clinical trials regarding the relative efficacies of particular agents (1, 32, 33). In general, the manner in which antidepressive agents are implemented for dysthymia is similar to that for episodes of major depressive disorder; responses to antidepressant medications by patients with dysthymia and chronic major depressive disorder have been shown to be comparable to the responses by patients with major depressive disorder episodes (34).

Psychotherapy, including interpersonal therapy, cognitive behavioral therapy, cognitive therapy, and behavior therapy, has also been shown to be effective in treating patients with dysthymia and chronic major depressive disorder, although responses have been somewhat smaller than when these modalities are used to treat patients with major depressive disorder (34, 35). Individuals with chronic major depressive disorder may also be considered for psychodynamic psychotherapy in order to examine psychological factors that may maintain the depressed disposition. The combination of psychotherapy and medication has been shown to be more effective than medication alone in patients with dysthymia (36–38).

Double depression is the term used to describe the common condition of a patient with chronic dysthymia who suffers the additional burden of a more severe and pervasive episode of major depressive disorder. Antidepressant medication treatment has been shown to reverse not only the acute major depressive disorder episode but also the underlying chronic dysthymia (39).

9. Comorbid personality disorders

People with any of a variety of personality disorders, including obsessive-compulsive, avoidant, dependent, and borderline disorders, are prone to episodes of major depressive disorder (40). Clinical experience indicates that patients with narcissistic personality disorder are also particularly vulnerable to episodes of major depressive disorder. Patients with major depressive disorder who meet criteria for borderline personality disorder frequently exhibit atypical features, including mood reactivity, and may be more likely to respond to MAOIs and SSRIs than to tricyclic antidepressants (41). Patients with virtually any form of personality disorder exhibit less satisfactory antidepressant medication treatment response, in terms of both social functioning and residual major depressive disorder symptoms, than do individuals without personality disorders (42). Psychodynamic psychotherapy, including psychoanalysis, may be beneficial in modifying the personality disorder in selected patients. Antisocial personality traits tend to interfere with treatment adherence and development of a psychotherapeutic relationship.

10. Seasonal major depressive disorder

Some individuals suffer annual episodes of major depressive disorder with onset in the fall or early winter, usually at the same time each year. Some of these patients suffer manic or hypomanic episodes as well. The major depressive disorder episodes frequently have atypical features such as hypersomnia and overeating. The entire range of treatments for major depressive disorder may also be used to treat seasonal affective disorder, either in combination with or as an alternative to light therapy. As a primary form of treatment, light therapy may be recommended as a time-limited trial (43), primarily in outpatients with clear seasonal patterns. In patients with more severe forms of seasonal major depressive disorder, its use is considered adjunctive to psychopharmacologic intervention.

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 human relationship or life role. Major depressive disorder episodes following life stresses are no less likely than other depressive episodes to either require or benefit from antidepressant medication treatment. 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. 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 and is commonly accompanied by the signs and symptoms of major depressive disorder. Historically, such depressive manifestations have been regarded as normative, and presentations otherwise diagnosable as major depressive disorder are therefore diagnosed in DSM-IV as uncomplicated bereavement when they begin within the first 3 months of the loss (44). Data indicate that almost one-quarter of bereaved individuals meet the criteria for major depressive disorder at 2 months and again at 7 months and that many of these people continue to do so at 13 months (45). Individuals with more prolonged major depressive disorder manifestations tend to be younger and to have a history of prior episodes of major depressive disorder. Antidepressant medications or psychotherapy should be used when the reaction to a loss is particularly prolonged and psychopathology and functional impairment persist.

3. Family distress

The recognition of a problem in the family setting is important in that such a situation constitutes an ongoing stressor that may hamper the patient's response to treatment. Ambivalent, abusive, rejecting, or highly dependent family relationships may particularly predispose an individual to major depressive disorder. Such families should be evaluated for family therapy, which may be used in conjunction with individual and pharmacologic 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.

4. Cultural factors

Specific cultural variables may hamper the accurate assessment of major depressive disorder symptoms. An appreciation by the therapist of cultural variables is critical in the accurate diagnosis of major depressive disorder and in the selection and conduct of psychotherapy and pharmacotherapy. There is evidence that the expression of major depressive disorder symptoms may vary among cultures, especially the tendency to manifest somatic and psychomotor symptoms (46). Ethnic groups may also differ in their pharmacotherapeutic responses to antidepressant medications (47, 48). The language barrier has also been shown to severely impede accurate psychiatric diagnosis and effective treatment (49, 50).

5. Children and adolescents

The clinical presentation of depression in children and adolescents can differ significantly from that of adults and will vary with the child's age. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss. Adolescents may present with somatic complaints, self-esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior. A careful assessment of the risk of suicide is necessary and should include an evaluation of risk factors such as recent loss or termination of a relationship, especially by suicide, disciplinary action, or alcohol or other substance abuse. A variety of informants should be used in the evaluation, including parents and teachers.

While a review of medication treatment studies (1) and a number of treatment recommendations (51) for children and adolescents are available, the evidence base for guiding treatment decisions for youth with major depressive disorder is quite limited. As a result, treatment decisions are frequently based on clinical consensus and the extrapolation of data from adults. It is important to be aware, however, that the extrapolation of adult data to children and adolescents is fraught with problems. For example, medications shown to be effective in adults have not always been found to be effective in children, and medications shown to be safe in adults have raised some serious safety concerns in children.

6. Older age

Considerations that go into choosing among psychotherapy, pharmacotherapy, and ECT for the elderly are essentially the same as for younger patients (52). The elderly typically display more vegetative signs and cognitive disturbance and complain less of subjective dysphoria than do their younger counterparts; major depressive disorder may consequently be misattributed to physical illness, dementia, or the aging process itself. It is recognized, however, that major depressive disorder and general medical illness frequently coexist in this age group, and those undergoing their first major depressive disorder episode in old age should be regarded as possibly harboring an as yet undiagnosed neurological or other general medical disorder that is responsible for the major depressive disorder condition. Some medications commonly prescribed for the elderly (e.g., beta-blockers) are thought to be risk factors for the development of major depressive disorder. The clinician should carefully assess whether a given agent contributed to the

major depressive disorder before prematurely altering what may be a valuable medication regimen. Major depressive disorder is a common complication of cerebral infarction, especially in the anterior left hemisphere (53).

Although elderly patients typically require a lower oral dose than younger patients to yield a particular blood level and tolerate a given blood level less well, the blood levels at which antidepressant medications are maximally effective appear to be the same as for younger patients (54). Elderly patients are particularly prone to orthostatic hypotension and cholinergic blockade; for this reason, fluoxetine, sertraline, bupropion, desipramine, and nortriptyline are frequently chosen rather than amitriptyline, imipramine, and doxepin. Weight loss may be especially problematic in the elderly. When this is the case, it might be beneficial to use an antidepressant that causes weight gain (see Table 7). 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. ECT should be considered for many of these patients. A recent study has shown that antidepressant medication (nortriptyline) and interpersonal therapy are effective maintenance therapies for elderly patients with recurrent major depressive disorder; a trend toward superior response was observed for combined pharmacotherapy and psychotherapy compared to pharmacotherapy alone (52).

7. Gender and pregnancy

The risks of certain adverse effects from treatments may also differ by gender. Caution is advised in the prescription of trazodone to men because of the risk of priapism. Older men are at risk for prostatic hypertrophy, making them particularly sensitive to medication effects on the bladder outlet. While both men and women may experience decreased libido or anorgasmia while taking SSRIs, men may also experience ejaculatory dysfunction. Some women who are taking birth control pills require higher doses of tricyclic antidepressant medications because of the induction of the hepatic enzymes responsible for medication metabolism.

The diagnostic assessment for women, in particular, should include a detailed inquiry regarding reproductive life history, including menstruation, menopause, birth control, and abortions. History of experiences of sexual and physical abuse, posttraumatic stress disorder, and treatment, if any, should be obtained.

Major depressive disorder occurring during pregnancy is a difficult therapeutic problem. Women of childbearing potential in psychiatric treatment should be carefully counseled as to the risks of becoming pregnant while taking psychotropic medications. Whenever possible, a pregnancy should be planned in consultation with the psychiatrist so that medication may be discontinued before conception if feasible. Antidepressant medication treatment should be considered for pregnant women who have major depressive disorder, as well as for those women who are in remission from major depressive disorder, receiving maintenance medication, and deemed to be at high risk for a recurrence if the medication is discontinued. The risks of treatment with medications must be weighed against the risks of alternative treatments, as well as the risks to the woman if the major depressive disorder is not effectively treated. These risks have recently been reviewed (55).

Specific concerns about the risks of untreated major depressive disorder in pregnancy include the possibility of low birth weight secondary to poor maternal weight gain (or frank weight loss). Suicidality, as well as the potential for long-term hospitalization, marital discord, the inability to engage in appropriate obstetrical care, and difficulty caring for other children must also be considered.

The considerations for the use of psychotherapy during pregnancy are identical to those relevant to nonpregnant patients, with the caveat that the risks of a delay in effectiveness may need to be considered in the context of the mother's safety as well as the safety of her fetus.

TABLE 7. Potential Treatments for Side Effects of Antidepressant Medications

Side Effect	Antidepressant(s) Associated With Effect	Treatment
Cardiovascular		
Orthostatic hypotension	Tricyclic antidepressants; trazodone; nefazodone; MAOIs	Lower dose; discontinue medication; fludrocortisone; add salt to diet
Reduced cardiac output	Tricyclic antidepressants	Discontinue medication
Arrhythmias	Tricyclic antidepressants	Discontinue medication
Hypertension	Venlafaxine	Lower dose; discontinue medication
Hypertensive crisis	MAOIs	Discontinue medication; intravenous phentolamine
Increase in cholesterol	Mirtazapine	Lower dose; discontinue medication
Anticholinergic		
Dry mouth	Tricyclic antidepressants; reboxetine	Pilocarpine oral rinse; gum; candy
Constipation	Tricyclic antidepressants; reboxetine	Hydration; bulk laxatives
Urinary hesitancy	Tricyclic antidepressants; reboxetine	Bethanechol
Visual changes	Tricyclic antidepressants; reboxetine	Pilocarpine eye drops
Delirium	Tricyclic antidepressants	Discontinue medication; antipsychotic medication
Sedation	Tricyclic antidepressants; trazodone; nefazodone; mirtazapine	Bedtime dosing
Weight gain	Tricyclic antidepressants; mirtazapine; MAOIs	Lower dose; change to secondary amine (if tricyclic antidepressant required); discontinue medication
Nausea, vomiting	SSRIs; bupropion, sustained release; venlafaxine, extended release	Lower dose; discontinue medication
Insomnia	SSRIs; bupropion; reboxetine	Lower dose; discontinue medication; morning dosing; trazodone at bedtime
Activation	SSRIs; venlafaxine	Lower dose; discontinue medication
Neurological		
Myoclonus	Tricyclic antidepressants; MAOIs	Lower dose; discontinue medication; clonazepam
Extrapyramidal symptoms; tardive dyskinesia	Amoxapine; SSRIs	Lower dose; discontinue medication
Seizures	Bupropion; amoxapine	Lower dose; discontinue medication; antiepileptic medication
Headaches	SSRIs; bupropion	Lower dose; discontinue medication
Sexual side effects		
Arousal, erectile dysfunction	Paroxetine; venlafaxine	Lower dose; discontinue medication; sildenafil; yohimbine; ginkgo; methylphenidate; dextroamphetamine; pemoline
	Tricyclic antidepressants; SSRIs	Lower dose; discontinue medication; sildenafil; yohimbine; ginkgo; bethanechol; neostigmine

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

Side Effect	Antidepressant(s) Associated With Effect	Treatment
Sexual side effects *(continued)*		
Orgasm dysfunction	SSRIs; venlafaxine	Lower dose; discontinue medication; granisetron; amantadine; cyproheptadine; sildenafil
	MAOIs; tricyclic antidepressants	Lower dose; discontinue medication; cyproheptadine; amantadine
Priapism	Trazodone	Discontinue medication; surgical correction
Serotonin syndrome	SSRIs; MAOIs; venlafaxine	Discontinue medication
Agranulocytosis	Mirtazapine	Discontinue medication; monitor white blood cell count, granulocyte colony–stimulating factor

Wisner et al. reviewed the risks associated with the use of antidepressant medications during pregnancy (55). Potential risks that should be considered include intrauterine death, morphologic teratogenicity, growth impairment, behavioral teratogenicity, and neonatal toxicity. Wisner et al. also reviewed the limitations of the available database and the basic principles to be used in treating pregnant women with antidepressants. In particular, dose requirements change during pregnancy because of changes in volume of distribution, hepatic metabolism, protein binding, and gastrointestinal absorption. Although clinicians need to keep abreast of new data as they become available, at this time there is no evidence that tricyclic antidepressants, fluoxetine, or newer SSRIs cause either intrauterine death or major birth defects. However, in one large study (56), three or more minor physical anomalies occurred more commonly in infants exposed to fluoxetine than in a comparison group. This study also demonstrated that fetuses exposed to fluoxetine after 25 weeks' gestation had lower birth weights, which were associated with lower maternal weight gain.

The area of behavioral teratogenicity remains the major area of concern when prescribing psychoactive medications to pregnant women. Both tricyclic antidepressants and fluoxetine have been studied, and the results provide no evidence for effects on cognitive function, temperament, or general behavior. However, replication studies, as well as data regarding other newer antidepressants, are needed.

Neonatal withdrawal syndromes have been reported in babies exposed, in utero, to tricyclic antidepressants, fluoxetine, and sertraline. Given these data, it is recommended that consideration be given to using either a tricyclic antidepressant or an SSRI that has been studied in pregnant women. If a tricyclic antidepressant is to be used, nortriptyline should be particularly considered because of its relatively low anticholinergic effects, long history of use, and well-studied relationship between plasma concentration and therapeutic effect (55). When antidepressants are used, maternal weight gain should be carefully monitored, and consideration should be given to gradually tapering the medication 10–14 days before the expected date of delivery. If this is done, and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy. In selected cases not responding to or unsuitable for medication, for patients with major depressive disorder with psychotic features, or for individuals electing to use this modality as a matter of preference after having weighed the relative risks and benefits, ECT may be used as an alternative treatment; the current literature supports the safety for mother and fetus, as well as the efficacy of ECT during pregnancy (57).

Several major depressive disorder conditions may follow childbirth (58). The transient 7–10-day depressive condition referred to as postpartum blues typically is too mild to meet the criteria for major depressive disorder and does not require medication. It is optimally treated by

reassuring the patient of its brief nature and favorable outcome. Puerperal psychosis is a more severe disorder complicating 1–2 per 1,000 births; more than one-half of the episodes of this type meet the criteria for major depressive disorder (59), and many patients who have had episodes of this type ultimately prove to have bipolar disorder. Major depressive disorder, and especially major depressive disorder with psychotic features, can seriously interfere with the new mother's ability to provide physically and emotionally appropriate care for her baby. The woman's parenting skills for both the newborn baby and any other children in her care must be carefully assessed. Women with postpartum psychotic major depressive disorder may have homicidal impulses toward the newborn; for this reason, careful assessment of homicidal as well as suicidal ideation, intention, or plans is important. Women whose maintenance antidepressant medication treatment was discontinued during pregnancy appear to be particularly at risk for recurrence of major depressive disorder; such individuals should have their medications restored after delivery, in the absence of a contraindication.

Major depressive disorder in the postpartum period should be treated according to the same principles delineated for other types of major depressive disorder. However, when a woman decides to nurse, the potential benefits to the mother of using antidepressant medications should be balanced against the potential risks to the newborn inherent in the possibility of receiving some antidepressant in the breast milk; mothers should be counseled regarding the relative risks and benefits when making treatment decisions (60, 61).

8. Family history

The presence of a positive 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.

The presence in a depressed patient of a positive family history of bipolar disorder or acute psychosis probably increases the chances that the patient's own major depressive disorder is a manifestation of bipolar rather than unipolar disorder and that antidepressant medication therapy may incite a switch to mania (62). Patients with such a family history should be particularly closely questioned regarding a prior history of mania or hypomania, since lithium used alone or in conjunction with another antidepressant medication is particularly likely to exert a beneficial effect in patients with bipolar disorder who have a major depressive episode. Patients with major depressive disorder with a family history of bipolar disorder should be carefully observed for signs of a switch to mania during antidepressant medication treatment.

C. TREATMENT IMPLICATIONS OF CONCURRENT GENERAL MEDICAL DISORDERS

1. Asthma

Individuals with asthma who receive MAOIs should be cautioned regarding interactions with sympathomimetic bronchodilators, although other antiasthma agents appear to be safe. Other antidepressant medications may be used for patients with asthma without fear of interaction.

2. Cardiac disease

The presence of specific cardiac conditions complicates or contraindicates certain forms of antidepressant medication therapy, notably use of tricyclic agents; the cardiac history should therefore be carefully explored before the initiation of medication treatment. Although tricyclic antidepressants have been used effectively to treat major depressive disorder in patients with some forms of ischemic heart disease (63), psychiatrists should take particular care in using tricyclics 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 (64–70). SSRIs, bupropion, and ECT appear to be safer for patients with preexisting cardiac disease, although the latter may require consultation with a specialist and treatment modification before use (63, 71–77). MAOIs do not adversely affect cardiac conduction, rhythm, or contraction but may induce orthostatic hypotension and also run the risk of interacting adversely with other medications that may be taken by such patients. There is anecdotal evidence that trazodone may induce ventricular arrhythmias, but the agent appears to be safe for the overwhelming majority of patients.

A depressed patient with a history of any cardiac problem should be monitored for the emergence of cardiac symptoms, ECG changes, or orthostatic blood pressure decrements. Consultation with the patient's cardiologist before and during antidepressant medication treatment may be advisable and is especially advisable during any treatment for a patient who has recently had a myocardial infarction.

3. Dementia

Treatment of major depressive disorder in the cognitively impaired patient requires the involvement of clinicians in the patient's pharmacotherapy, supervision, and monitoring; this involvement may entail education of home health aides, nursing home providers, and others. Individuals with dementia are particularly susceptible to the toxic effects of muscarinic blockade on memory and attention. Therefore, individuals suffering from 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. Alternatively, some patients do well given stimulants in small doses. ECT is also effective in major depressive disorder superimposed on dementia, and it should be used if medications are contraindicated, 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). Practitioners should be aware that a transient worsening of the patient's cognitive status may occur in such cases (72, 75, 78).

4. Epilepsy

Although many antidepressant medications lower the seizure threshold and theoretically exert a dose-dependent adverse effect on seizure control in patients with major depressive disorder with epilepsy, 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. Consideration should be given to concomitant prescription of an antiepileptic (or elevating the dose of an existing antiepileptic).

5. Glaucoma

Medications with anticholinergic potency may precipitate acute narrow-angle glaucoma in susceptible individuals (i.e., those with shallow anterior chambers) (79). 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. Agents lacking anticholinergic activity (bupropion, sertraline, fluoxetine, and trazodone) avoid this liability.

6. Hypertension

Antihypertensive agents and tricyclic antidepressant medications may interact to either intensify or counteract the effect of the antihypertensive therapy. 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 tricyclic antidepressants and trazodone. Tricyclic antidepressants may antagonize the therapeutic actions of guanethidine, clonidine, or α-methyldopa. Concurrent antihypertensive treatment, especially with diuretics, increases the likelihood that

tricyclic antidepressants, trazodone, or MAOIs will induce symptomatic orthostatic hypotension. Beta-blockers, especially propranolol, may be a cause of major depressive disorder in some patients; individuals who have become depressed after initiation of treatment with one of these medications should be changed to another antihypertensive regimen. Dose-dependent elevations in blood pressure with venlafaxine are usually mild, although more severe elevations have been observed (80), making this agent less preferable in patients with hypertension.

7. Obstructive uropathy

Prostatism and other forms of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects. Benzodiazepines, trazodone, and MAOIs may also retard bladder emptying. The antidepressant medications with the least propensity to do this are SSRIs, bupropion, and desipramine.

8. Parkinson's disease

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. 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 (81). MAOIs (other than selegiline, also known as L-deprenyl, a selective type B MAOI recommended in the treatment of Parkinson's disease) may adversely interact with L-dopa products (82). Selegiline loses its specificity for MAO-B in doses greater than 10 mg/day and may induce serotonin syndrome when given in higher doses in conjunction with serotonin-enhancing antidepressant medications. Major depressive disorder, which occurs to some degree in 40%–50% of patients with Parkinson's disease, may be related to the alterations of serotonergic and noradrenergic systems that occur in this disorder. There is no evidence favoring any particular antidepressant medication from the standpoint of therapeutic efficacy in patients with Parkinson's disease complicated by major depressive disorder. 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. ECT exerts a transient beneficial effect on the symptoms of idiopathic Parkinson's disease in many patients (83).

PART B:
BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

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

DSM-IV criteria for major depressive episode and major depressive disorder are listed in Table 8.

A. SPECIFIC FEATURES OF DIAGNOSIS

1. Severity

An episode of major depressive disorder may be classified as mild, moderate, or severe. Mild episodes are characterized by little in the way of symptoms beyond the minimum required to make the diagnosis and by minor functional impairment. Moderate episodes are characterized by the presence of symptoms in excess of the bare diagnostic requirements and by greater degrees of functional impairment. Severe episodes are characterized by the presence of several symptoms in excess of the minimum requirements and by the symptoms' marked interference with social and/or occupational functioning. In the extreme, afflicted individuals may be totally unable to function socially or occupationally or even to feed or clothe themselves or to maintain minimal personal hygiene. The nature of the symptoms, such as suicidal ideation and behavior, should also be considered in assessing severity.

2. Melancholia

The melancholic subtype is a severe form of major depressive disorder with characteristic somatic symptoms, and it is believed to be particularly responsive to pharmacotherapy and ECT.

3. Psychotic features

Major depressive disorder may be accompanied by hallucinations or delusions; these may be congruent or noncongruent with the depressive mood.

4. Dysthymia

The differential diagnosis of dysthymia and major depressive disorder is particularly difficult, since the two disorders share similar symptoms and differ primarily in duration and severity. Usually major depressive disorder consists of one or more discrete major depressive episodes that can be distinguished from the person's usual functioning, whereas dysthymia is characterized by a chronic mild depressive syndrome that has been present for at least 2 years. If the initial onset of what appears to be dysthymia directly follows a major depressive episode, the appropriate diagnosis is major depressive disorder in partial remission. The diagnosis of dysthymia can be made following major depressive disorder only if there has been a full remission of the major depressive episode that has lasted at least 6 months before the development of dysthymia.

People with dysthymia frequently have a superimposed major depressive disorder, and this condition is often referred to as double major depressive disorder. Patients with double major depressive disorder are less likely to have a complete recovery than are patients with major depressive disorder without dysthymia.

B. EPIDEMIOLOGY

The Epidemiologic Catchment Area study indicates that major depressive disorder has a 1-month prevalence of 2.2% and a lifetime prevalence of 5.8% in Americans 18 years and older (84). Other studies estimate the lifetime prevalence to be as high as 26% for women and 12% for men. The illness is 1.5 to 3 times as common among those with a first-degree biological relative affected with the disorder as among the general population. Major depressive disorder is frequently accompanied by comorbid conditions. For example, in one study of patients with major depressive disorder under the care of psychiatrists in the United States, 84% had at least one comorbid condition: 61% had a co-occurring axis I condition, 30% a comorbid axis II condition, and 58% a comorbid axis III condition (85). Frequently a major depressive episode follows a psychosocial stressor, particularly death of a loved one, marital separation, or the ending of an important relationship. Childbirth sometimes precipitates a major depressive episode. Pa-

TABLE 8. DSM-IV 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 by either 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

TABLE 8. DSM-IV 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

Source. Reprinted from *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition. Washington, DC, American Psychiatric Association, 1994. Copyright © 1994, American Psychiatric Association.

tients with major depressive disorder identified in psychiatric settings tend to have episodes of greater severity and to have recurrent forms of major depressive disorder and also are more likely to have other mental disorders than are subjects from the community and primary care settings.

C. NATURAL HISTORY AND COURSE

The average age at onset is the late 20s, but the disorder may begin at any age. The 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 cases, however, a major depressive disorder may develop suddenly (e.g., when associated with severe psychosocial stress). The duration of a major depressive episode is also variable. Untreated, the episode typically lasts 6 months or longer. Some patients with major depressive disorder will eventually have a manic or hypomanic episode and will then be diagnosed as having bipolar disorder.

1. Recurrence

Although some people have only a single episode of major depressive disorder, with full return to premorbid functioning, it is estimated that from 50% to 85% of the people who have such an episode will eventually have another episode, at which time the illness will meet the criteria for recurrent major depressive disorder (86). People with major depressive disorder superimposed on dysthymia are at greater risk for having recurrent episodes of major depressive disorder than those without dysthymia.

The course of recurrent major depressive disorder is variable. 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 grow older.

2. Interepisode status

Functioning usually returns to the premorbid level between episodes. In 20%–35% of the cases, however, there are persistent residual symptoms and social or occupational impairment. Patients who continue to meet the criteria for a major depressive episode throughout the course of the disturbance are considered to have the chronic type, whereas those who remain symptomatic are considered to be in partial remission.

3. Seasonal pattern

A seasonal pattern of major depressive disorder is characterized by a regular temporal relationship between the onset and remission of symptoms and particular periods of the year (e.g., in

the northern hemisphere, regular appearance of symptoms between the beginning of October and the end of November and regular remission from mid-February to mid-April). Patients should not receive this diagnosis if there is an obvious effect of seasonally related psychosocial stressors, e.g., seasonal unemployment.

4. Complications

The most serious complications of a major depressive episode are suicide and other violent acts. Other complications include marital, parental, social, and vocational difficulties (87). The illness, especially in its recurrent and chronic forms, may cause distress for 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 (88). Major depressive disorder episodes are associated with occupational dysfunction, including unemployment, absenteeism, and decreased work productivity (89). Major depressive disorder may also complicate recovery from other medical illnesses. Major depressive disorder has been demonstrated to be a major risk factor in the post-myocardial-infarction period.

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

Successful treatment of patients with major depressive disorder is promoted by a thorough assessment of the patient's symptoms; past general medical and psychiatric history; psychological makeup and conflicts; life stressors; family, psychosocial, and cultural environment; and preference for specific treatments or approaches.

The psychiatrist's task is both to effect and to maintain improvement. Treatment consists of an acute phase, during which remission is induced; a continuation phase, during which remission is preserved; and a maintenance phase, during which the susceptible patient is protected against the recurrence of subsequent major depressive disorder episodes. Psychiatrists initiating treatment of a major depressive disorder episode have at their disposal a number of medications, a variety of psychosocial approaches, ECT, and light therapy. These various interventions may be used alone or in combination. Furthermore, the psychiatrist must decide whether to conduct treatment on an outpatient, partial hospitalization, or inpatient basis.

A. ACUTE PHASE SOMATIC TREATMENTS

1. Antidepressant medications

a) Goals

The goal of treatment with antidepressant medications in the acute phase is the remission of major depressive disorder symptoms. For cases of first-episode major depressive disorder uncomplicated by comorbid general medical illness or by special features such as atypical, psychotic, or bipolar symptoms, many antidepressant medications are available. Systematic data from clinical trials regarding the relative efficacy of different antidepressant medications are lacking. For most patients, antidepressant medications approved by the Food and Drug Administration (FDA) are generally considered equally effective, with response rates in clinical trials ranging from 50% to 75% of patients. However, among some subgroups of patients with major depressive disorder, ef-

ficacy may differ. Antidepressant medications also differ in their potential to cause particular side effects. Antidepressant medications have been grouped as follows: 1) tricyclic antidepressant medications, which for the purposes of this review also include the tetracyclic antidepressant medication maprotiline; 2) SSRIs, which include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram; 3) other antidepressant medications, including bupropion, nefazodone, trazodone, venlafaxine, mirtazapine, and reboxetine (for which FDA approval is anticipated); and 4) MAOIs, which include phenelzine, tranylcypromine, and isocarboxazid.

b) Efficacy

Quantitative reviews of the efficacy of antidepressant medications for major depressive disorder have been performed, including the recent *Evidence Report on Treatment of Depression—Newer Pharmacotherapies* (1). This study examined 315 trials, lasting 6 weeks or longer, of newer pharmacotherapies for patients with depressive disorders. Additional details concerning the evidence of antidepressant medication efficacy that may be beyond the scope of this guideline can be obtained from such reviews.

Interpreting data from clinical trials on the efficacy of pharmacotherapy for major depressive disorder can be complicated by several issues. 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 explain observed treatment effects in poorly controlled trials as well as make detection of true treatment effects difficult in well-controlled trials. It is also important to consider both whether trials were blinded and whether in "blinded" trials, 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. Data often come from short-term (6- to 12-week) efficacy trials that may not reveal whether treatments are effective over the medium and long term. Lastly, it is important to consider whether publication bias against reporting of negative studies could affect the perception of overall treatment effectiveness.

(1) Tricyclic antidepressants

Since the first trial in which a tricyclic compound (imipramine) was shown to improve major depressive disorder symptoms (90), hundreds of subsequent randomized controlled trials have demonstrated the efficacy of this class as a treatment for major depressive disorder (1). Heterocyclic antidepressant medications, including tricyclics and tetracyclics, have been found to be statistically significantly superior to placebo in approximately 75% of studies (91); several reviews suggest that approximately 50%–75% of patients with major depressive disorder treated with heterocyclic antidepressant medications respond compared to 25%–33% treated with placebo (92–95). The efficacy of individual agents and subclasses of tricyclics (e.g., secondary amines or tertiary amines) appears to be comparable.

Results of some investigations have suggested that tricyclic antidepressants may possess superior efficacy among subgroups of patients with severe major depressive disorder symptoms (91, 96–99). Some studies have also suggested that in major depressive disorder marked by melancholic features, tricyclic antidepressants may be additionally effective (100, 101) as well as superior to SSRIs (102, 103); however, not all research supports these findings (104).

(2) Selective serotonin reuptake inhibitors

SSRIs currently available include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. A large body of literature containing approximately 50 randomized, placebo-controlled trials supports the premise that SSRIs are superior to placebo in the treatment of major depressive dis-

order. In over 50 investigations the effectiveness of SSRIs has been compared to that of other antidepressant medications, mainly tricyclic antidepressants; in these trials, SSRIs have generally had comparable efficacy to antidepressant medications from other classes (1, 105, 106). In general, significant differences in efficacy between individual SSRIs have not been observed.

There is some evidence that SSRIs may be more effective than tricyclic antidepressants for subgroups of patients with atypical symptoms of major depressive disorder (e.g., mood reactivity, hypersomnia, hyperphagia, and hypersensitivity to rejections) (23). SSRIs have also been shown to be helpful for some patients who have not responded to tricyclic antidepressants (107).

(3) Other antidepressant medications

Several other antidepressant medications are available that differ structurally or in their pharmacologic action from medications in the categories just described. Trazodone is the medication from this group for which the most data on efficacy exists. In most trials, trazodone has had superior efficacy relative to placebo; however, its efficacy relative to other antidepressant medications remains controversial. Although data from some controlled trials suggest comparable efficacy to tricyclic antidepressants (108, 109), other investigations suggest trazodone may possess inferior efficacy relative to other antidepressant medications (1, 110, 111), particularly in subgroups with severe major depressive disorder symptoms or prominent psychomotor retardation (112, 113).

Nefazodone has an analogous structure to trazodone but somewhat different pharmacologic properties. In controlled trials, nefazodone has had superior efficacy to placebo; in five trials, nefazodone has been found to have comparable efficacy to tricyclic antidepressants (1, 114, 115). Some studies suggest that nefazodone may have an optimal therapeutic dose range corresponding to approximately 300–600 mg/day (115, 116).

Bupropion appears to inhibit the reuptake of both norepinephrine and dopamine, although its mechanism of action remains unclear. Trial data have shown that bupropion is superior to placebo (117) and generally comparable in efficacy to both tricyclic antidepressants (1, 118–121) and SSRIs (122).

Venlafaxine and mirtazapine appear to act through inhibition of reuptake of both norepinephrine and serotonin. Both have been demonstrated to be superior to placebo; venlafaxine and mirtazapine have each been shown in four trials to possess generally comparable efficacy to tricyclic antidepressants (1, 110, 123–128). Results from one trial suggest a positive relationship between the effective dose of venlafaxine and the severity of major depressive disorder—favorable responses were achieved with lower doses in milder major depressive disorders, whereas higher doses were more efficacious in severe major depressive disorder (129).

Reboxetine is a new selective noradrenaline reuptake inhibitor for which approval from the FDA is expected. In four trials, reboxetine has been shown to be more effective than placebo; in 6 trials against active treatment, reboxetine has been found to possess at least comparable effectiveness as tricyclic antidepressants and SSRIs (1, 130).

(4) Monoamine oxidase inhibitors

MAOIs that have been used as antidepressant medications include phenelzine, tranylcypromine, and isocarboxazid. MAOIs 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 tricyclic antidepressants to be superior, MAOIs are now considered to have comparable efficacy to tricyclic antidepressants for typical cases of major depressive disorder (131–136). There are no significant differences in efficacy among the MAOIs.

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 (19, 137, 138). MAOIs have also been shown to be effective treatments for some patients who have failed other antidepressant medication trials (132, 136, 139, 140).

c) Side effects

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 between classes of antidepressant medications, between subclasses, and between individual agents. Prominent and clinically relevant side effects associated with particular classes, subclasses, and individual medications are reviewed in Table 7.

(1) Tricyclic antidepressants

i. Cardiovascular effects

Tricyclic antidepressants can cause a number of cardiovascular side effects through α-adrenergic blockade, including tachycardia or orthostatic hypotension. Side effects such as orthostatic hypotension may in turn lead to events such as dizziness, falls, or fractures. Secondary amines such as nortriptyline or desipramine cause less α-adrenergic blockade and may offer advantages over tertiary amines (69). Salt depletion, whether voluntary or a result of diuretic treatment, may contribute to orthostatic hypotension. If there is no medical contraindication, patients with symptomatic orthostatic hypotension should be cautioned against extreme dietary salt restriction.

Tricyclic antidepressant medications act similarly to class I antiarrhythmic agents such as quinidine, disopyramide, and procainamide by prolonging cardiac repolarization and depressing fast sodium ion channels (141). Both secondary and tertiary amines have been documented to suppress ventricular premature depolarizations (64, 67). Combinations of tricyclic antidepressants 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 tricyclic medication therapy should be under careful medical supervision. Tricyclic antidepressants may also provoke arrhythmias in patients with subclinical sinus node dysfunction; for example, in patients with tachyarrhythmias, treatment with tricyclic antidepressants may on occasion provoke bradyarrhythmias (65). Among patients with preexisting but asymptomatic conduction defects, such as interventricular conduction delay and bundle-branch block, tricyclic antidepressants may induce symptomatic conduction defects and symptomatic orthostatic hypotension (69). Individuals with prolonged QT intervals, whether preexistent or medication-induced, are predisposed to the development of ventricular tachycardia (70). It has also been reported that patients with normal pretreatment ECG results may develop atrioventricular block that reverts to normal after discontinuation of antidepressant medication treatment (69).

For most patients, tricyclic antidepressants exert no appreciable effect on ventricular ejection fraction (142); rarely (and usually in patients with marked baseline disturbances of myocardial function), tricyclic antidepressants may exert a deleterious effect on ejection fraction (66, 68).

ii. Anticholinergic side effects

All tricyclic antidepressant medications have some degree of antimuscarinic action; tertiary amine tricyclic antidepressants produce the most anticholinergic side effects, whereas the newer secondary amines, desipramine and nortriptyline, have less antimuscarinic activity. The most common undesirable consequences of muscarinic blockade are dry mouth, impaired ability to focus 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. Urinary hesitation may be treated by prescribing bethanechol, 200 mg/day (in divided doses to avoid symptoms of cholinergic excess, principally abdominal cramps, nausea, and diarrhea). Dry mouth may be counteracted by advising the patient to use sugarless gum or candy

or by prescribing an oral rinse of 1% pilocarpine used three or four times daily; oral bethanecol may also be effective. Constipation is best dealt with through 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 may also precipitate anticholinergic delirium, particularly in patients who are elderly or medically compromised.

iii. Sedation

Tricyclic antidepressants also have affinity for histaminergic receptors and produce varying degrees of sedation. In general, tertiary amines cause greater sedation, whereas secondary amines cause less. 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.

iv. Weight gain

Tricyclic antidepressants have the capacity to induce weight gain, possibly through their histaminergic properties. The degree of weight gain appears to vary by agent (e.g., greater weight gain with amitriptyline and less with desipramine), be dose dependent, and be reversible with cessation of tricyclic antidepressant therapy.

v. Neurological effects

Tricyclic antidepressants can induce mild myoclonus (143). 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 the myoclonus is not symptomatic, the agent may be continued without a change in dose. If the myoclonus is symptomatic 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. A toxic confusional state has been identified in some patients with high blood levels of tricyclic antidepressant medications, and it responds to simply lowering the dose (144). Amoxapine, a tricyclic antidepressant with antipsychotic properties, can also cause extrapyramidal side effects and tardive dyskinesia. In overdoses, tricyclic antidepressants can precipitate seizures.

vi. Medication interactions

Medications that induce hepatic microsomal enzymes, such as carbamazepine or barbiturates, will cause a decrease in serum tricyclic antidepressant level. On the other hand, drugs such as antipsychotic medications or SSRIs can reduce the metabolism and clearance of tricyclic antidepressants and raise tricyclic antidepressant levels. Tricyclic antidepressants can also alter the pharmacokinetics or pharmacodynamics of other medications; for example, tricyclic antidepressants can cause a lowering of valproate levels and reduce the activity of clonidine. Therefore, adjustments in medication doses may be necessary when tricyclic antidepressants are administered concomitantly with other drugs for which there is an interaction. Potentially dangerous interactions, including hypertensive crises, can develop when tricyclic antidepressants are administered with MAOIs, norepinephrine, or epinephrine.

(2) Selective serotonin reuptake inhibitors

i. Gastrointestinal

SSRIs cause nausea, vomiting, and diarrhea to a greater extent than tricyclic antidepressant medications (145). These adverse events are generally dose dependent and tend to dissipate over the first few weeks of treatment.

ii. Activation/insomnia

In some patients, SSRIs may precipitate or exacerbate restlessness, agitation, and sleep disturbances. These side effects often attenuate with time. Anxiety may be minimized by introducing the agent at a low dose; insomnia may be effectively treated by the addition of trazodone, up to 100 mg at bedtime.

iii. 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 sexual dysfunction is a result of the antidepressant medication or the underlying major depressive disorder. If sexual dysfunction is determined to be a side effect of the antidepressant medication, a variety of strategies are available, including continuing treatment to assess whether the dysfunction will disappear with time, lowering the dose, discontinuing the antidepressant, or substituting another antidepressant such as bupropion (Table 7) (146). Specific pharmacologic treatments that can be added for arousal or erectile dysfunction include sildenafil, yohimbine, or neostigmine; specific medications that can be added for orgasm dysfunction include sildenafil, cyproheptadine, or amantadine (147).

iv. Neurological effects

SSRIs can initially exacerbate both migraine headaches and tension headaches. These effects tend to be transient and improve within the first few weeks of treatment. There is some suggestion that with continued treatment SSRIs may then actually help prevent and treat migraine headaches (148, 149). SSRIs have also been associated with extrapyramidal reactions, including akathisia, dystonia, parkinsonism, and tardive dyskinesia (150, 151). The occurrence of such extrapyramidal symptoms is generally very low but may be higher in older patients, especially those with Parkinson's disease.

v. Effects on weight

Fluoxetine has been shown to cause an initial reduction in weight but this tends to be gained back subsequently (152). The literature differs as to whether patients taking SSRIs beyond the acute phase do (153) or do not (154) experience weight gain as a medication side effect.

vi. Serotonin syndrome

SSRI use has been associated with the rare development of a syndrome due to an excess of 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 (155, 156). Although serotonin syndrome can occur with the use of SSRIs alone, it is usually associated with the simultaneous use of multiple serotonergic agents such as SSRIs together with MAOIs, fenfluramine, or dexfenfluramine.

vii. Drug interactions

As previously described, there can be a potentially lethal interaction between SSRIs and MAOIs: serotonin syndrome. It has been suggested that at least five half-lives elapse between the time an SSRI is stopped and an MAOI is started; for fluoxetine discontinuation, this corresponds to waiting approximately 5 weeks before starting an MAOI, whereas for discontinuation of other SSRIs it corresponds to waiting approximately 1 week before starting an MAOI (157). A 2-week waiting period has been suggested after discontinuing an MAOI before starting an SSRI.

SSRIs can also have variable effects on hepatic microsomal enzymes and therefore cause both increases and decreases in the blood levels of other medications.

(3) Other antidepressant medications

i. Trazodone

The most common side effect with trazodone is sedation; this side effect may allow trazodone to be used to advantage in patients with initial insomnia. Trazodone can also cause cardiovascular side effects including orthostasis. Although trazodone does not prolong cardiac conduction, there have been case reports of cardiac arrhythmias developing during trazodone treatment (158, 159). Trazodone can cause sexual side effects, including erectile dysfunction in men; in rare instances, this may lead to irreversible priapism requiring surgical correction (160).

ii. Nefazodone

Side effects observed with nefazodone treatment include dry mouth, nausea, and constipation. Although nefazodone lacks anticholinergic properties, blurred vision has been noted. Nefazodone may also cause sedation and orthostasis but not as severe as that observed with trazodone. Nefazodone is known to inhibit hepatic microsomal enzymes and can raise levels of concurrently administered medications such as certain antihistamines, benzodiazepines, and digoxin.

iii. Bupropion

Neurological side effects have been observed with bupropion treatment including headaches, tremors, and seizures. Risks of seizures can be reduced by avoiding high doses (e.g., using less than 450 mg/day), using divided dosing schedules (e.g., three times a day), and avoiding bupropion use in patients with risk factors for seizures. Bupropion also possesses dopaminergic activity and has been associated with the development of psychotic symptoms, including delusions and hallucinations. For these reasons, bupropion should be used cautiously in patients with psychotic disorders. Other side effects observed with bupropion treatment include insomnia and gastrointestinal upset.

iv. Venlafaxine

The side effects of venlafaxine have been likened to those seen with SSRIs, including nausea and vomiting, sexual dysfunction, and activation; like the side effects seen with SSRIs, those with venlafaxine can attenuate with continued use. Venlafaxine can also cause an increase in blood pressure. Because this increase is dose related, venlafaxine-induced hypertension may respond to dose reduction.

v. Mirtazapine

The most common side effects from mirtazapine include sedation, dry mouth, and weight gain. These tend to occur early and may attenuate with continued treatment. Mirtazapine has also been shown to increase serum cholesterol levels in some patients (161). Although agranulocytosis has been observed to occur in patients taking mirtazapine, its occurrence has been very rare. Routine monitoring of a patient's WBC count is not needed, although checking may be advisable in patients with signs or symptoms of infection.

vi. Reboxetine

The most frequently reported side effects in trials of reboxetine have been dry mouth, constipation, increased sweating, insomnia, urinary hesitancy/retention, impotence, tachycardia, and vertigo (162). In clinical trials done to date, few serious adverse events have been reported among patients treated with reboxetine.

(4) Monoamine oxidase inhibitors

i. Hypertensive crises

A hypertensive crisis can occur when a patient taking an MAOI ingests large amounts of tyramine or other pressor amines in foods or medications. This reaction is characterized by the acute onset of severe headache, nausea, neck stiffness, palpitations, profuse perspiration, and

confusion, possibly leading to stroke and death (163). Dietary restrictions include avoiding such foods as aged cheeses or meats, fermented products, yeast extracts, fava or broad beans, and overripe or spoiled foods. The list of medications that must be avoided includes all sympathomimetic and stimulant drugs as well as over-the-counter decongestants and cold remedies.

Some clinicians have recommended that patients carry nifedipine and, at the outset of a possible hypertensive crisis, take an oral dose of 10 mg before proceeding to the hospital (164); this practice has not been approved by the FDA, and further study of the safety and efficacy of this strategy is needed (165). Definitive treatment of hypertensive crises usually involves intravenous administration of phentolamine in an emergency room setting.

ii. Serotonin syndrome

This syndrome most commonly occurs when MAOIs are taken in close proximity to other serotonergic agents (166). When patients are being switched from an SSRI with a short half-life 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 switching from fluoxetine to an MAOI, a waiting period of at least 5 weeks is needed before the MAOI is started. The serotonin syndrome may also occur when venlafaxine is administered soon after an MAOI (167).

iii. Cardiovascular effects

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

iv. Weight gain

Weight gain is also commonly seen in patients treated with MAOIs. The likelihood of this side effect appears to vary with the agent used, with most weight gain seen with tranylcypromine and the least with phenelzine.

v. 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.

vi. Neurological effects

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

d) Implementation

Typical starting doses and typical effective adult dose ranges that have been used in short-term efficacy trials of antidepressant medications appear in Table 1. Initial doses should be incrementally raised as tolerated until a presumably therapeutic dose is reached. 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; for other antidepressant medications, studies have failed to show dose-response relationships (168–170). Therefore, the initial doses and usual adult doses in Table 1 are intended to serve as general guidelines, and actual doses may vary from individual to individual. In general, older patients, medically frail patients, or patients with 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. Doses will also be affected by the side effect profile of medications and the patient's ability to tolerate these.

In short-term efficacy trials, all antidepressant medications appear to require 4–6 weeks to achieve their maximum therapeutic effects (171, 172) (although some patients may show partial improvement by as soon as the end of the first week [173]). Therefore, adequacy of response cannot be judged until after this period of time. Patients should be alerted to this and instructed to continue taking their antidepressant medications throughout this initial period.

For some medications, particularly the tricyclic antidepressants nortriptyline, desipramine, and imipramine, blood drug levels have been shown to correlate with both efficacy and side effects. Although in most cases monitoring of serum antidepressant medication levels is not necessary, in some circumstances this can be very useful. These circumstances can include when patients have not responded to adequate doses of an antidepressant medication given for adequate durations; 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.

Some antidepressant medications, especially tricyclics, can be associated with significant morbidity and potentially mortality in overdose. 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, trazodone, nefazodone, bupropion, venlafaxine, or mirtazapine.

2. Failure to respond to pharmacotherapy in the acute phase

Adequate treatment with an antidepressant medication for at least 4–8 weeks is necessary before concluding that a patient is not responsive or only partially responsive to a particular medication (172). Initial treatment with antidepressant medication fails to achieve a satisfactory response in approximately 20%–30% of patients with major depressive disorder; poor treatment response has been found to be not just the result of inadequate treatment but also a consequence of inappropriate diagnoses; failure to appreciate and remedy coexisting general medical conditions, psychiatric disorders, or complicating psychosocial factors; and nonadherence (174). For these reasons a first step in the care of a patient who has not responded to medication should be a review and reappraisal of the diagnosis, adherence, and neglected contributing factors, including general medical problems, alcohol or substance abuse or dependence, other psychiatric disorders, and general psychosocial issues impeding recovery. In cases where nonadherence or complicating psychosocial stressors are prominent, the addition of psychotherapy may be effective in enhancing response (152).

For patients whose treatment failure is not readily attributable to inappropriate diagnoses, poor adherence, or complicating conditions, a variety of therapeutic options are available, including maximizing the initial treatment, switching to another non-MAOI agent, augmenting antidepressant medications with other medications or psychotherapy, using an MAOI, and ECT (5). Empirical data concerning the relative efficacies of these strategies are limited.

a) Maximizing initial treatments

There is little evidence to support extending antidepressant medication trials beyond 6 weeks in patients who have shown no response. However, for patients who have shown a partial response, particularly those with features of personality disorders and prominent psychosocial stressors, extending the antidepressant medication trial (e.g., by 2–4 weeks) may allow up to one-third of patients to respond more fully (6).

Use of higher antidepressant medication doses is another strategy to maximize an initial treatment regimen, especially for patients who have received only modest doses or those who for pharmacodynamic reasons have low serum drug levels despite adequate doses and adherence.

Unfortunately, with the exception of nortriptyline, therapeutic windows for serum drug levels of most antidepressant medications are unknown. In addition, the strategy of increasing doses is often limited by the occurrence of more frequent and severe side effects.

b) Switching to a different non-MAOI agent

With the introduction of many newer antidepressant medications, switching to a different non-MAOI antidepressant medication has been a common strategy for patients who have failed a trial of pharmacotherapy. A few trials have been conducted in which patients who failed an initial antidepressant medication were switched to a non-MAOI antidepressant medication from the same pharmacologic class (e.g., from one tricyclic antidepressant to another) or to one from a different pharmacologic class (e.g., from a tricyclic antidepressant to an SSRI). Although results from these trials have been variable, up to 50% of patients have been found to respond to a second non-MAOI antidepressant medication trial (5). Data regarding the types of treatment-refractory patients who are most likely to benefit from particular switching strategies are limited. Although their use in this context has not been extensively evaluated, mood stabilizers such as carbamazepine and valproic acid have demonstrated some benefit in the treatment of medication-resistant major depressive disorder (175, 176).

c) Augmenting antidepressant medications with other treatments

Antidepressant medication augmentation strategies often consist of the use of multiple non-MAOI antidepressant medications. An SSRI in combination with a tricyclic agent, such as desipramine, has been reported to induce a rapid antidepressant medication response (50). However, SSRIs added to a tricyclic antidepressant medication may cause an increased blood level and delayed elimination of the tricyclic medication, predisposing the patient to tricyclic medication toxicity unless the dose of the tricyclic is reduced (177).

Lithium is another medication commonly used as an adjunct; other agents in use are thyroid hormone and stimulants. Lithium is felt by many experienced clinicians to be the most effective adjunct; it is reported to be useful in up to 50% of antidepressant medication nonresponders and is usually well tolerated (178). The interval before full response to adjunctive lithium is said to be in the range of several days to 3 weeks. The blood level required in this context has not yet been determined. If effective and well tolerated, lithium should be continued for the duration of treatment of the acute episode. Lithium may also increase the antidepressant medication effectiveness of carbamazepine (179). Thyroid hormone supplementation, even in euthyroid patients, may increase the effectiveness of antidepressant medication treatment (180). The dose proposed for this purpose is 25 μg/day of triiodothyronine, increased to 50 μg/day in a week or so in the event of continued nonresponse. The duration of treatment required has not been well studied. Case reports suggest that stimulant medications may be effective adjuncts to antidepressant medication therapy (181, 182). There are no clear guidelines regarding the length of time stimulants should be coadministered.

A rarely used strategy is the combined use of a tricyclic antidepressant medication and an MAOI. This combination has been shown to be effective in alleviating some severe medication-resistant major depressive disorders; however, the risk of toxic interactions necessitates careful monitoring (183, 184). The combined use of MAOIs and other antidepressant medications has in some circumstances led to serious untoward reactions characterized by delirium, hyperthermia, hyperreflexia, myoclonus, and death; the reaction is sometimes referred to as the serotonin syndrome and is thought to be the result of overly enhanced serotonergic transmission. Use of an MAOI in combination with a tricyclic antidepressant should probably not be considered until all other strategies for treatment-refractory patients have been exhausted; psychiatrists and patients choosing to use an MAOI and a tricyclic antidepressant should be well acquainted with the potential hazards and carefully weigh the relative risks and benefits of such a strategy.

Data indicating the relative efficacies of the various adjunctive treatments are generally lacking.

d) Using a monoamine oxidase inhibitor

The role of MAOIs in major depressive disorder has largely become that of a treatment for patients who have failed other pharmacotherapies. Studies have demonstrated the effectiveness of MAOIs in patients who have failed to respond to other antidepressant medications, particularly tricyclic antidepressants (185). However, the effectiveness of MAOIs relative to other strategies for treatment-resistant patients remains unclear. Great care must be taken when switching patients from another antidepressant medication to an MAOI and from an MAOI to other antidepressant medications because of the persistence of the effects of discontinued medications and their metabolites and the potential for toxic interactions. For example, if the clinician chooses to discontinue a monoamine uptake blocking antidepressant medication and substitute an MAOI, toxic interactions can best be avoided by allowing a 1- to 2-week washout period between medication trials. The long half-life of the SSRI fluoxetine and its metabolites necessitates a 5-week washout period before the use of an MAOI.

e) Using electroconvulsive therapy

ECT has the highest rate of response of any form of antidepressant treatment and should be considered in virtually all cases of moderate or severe major depressive disorder not responsive to pharmacologic intervention. Even medication-resistant patients may show at least a 50% likelihood of a satisfactory response to ECT (186). ECT may also be the strategy of choice for patients with major depressive disorder with psychotic symptoms who have not responded to an antidepressant medication plus antipsychotic medication. ECT is generally considered to be safer than many forms of combination antidepressant medication treatment, although data to support this are lacking. There is growing use of ECT combined with antidepressant medication to potentiate response, although only a small amount of data supporting this practice presently exists (72, 187–191). The safety of combining lithium and ECT has been questioned, although there are conflicting data (72, 192–195).

3. Electroconvulsive therapy

a) Efficacy

ECT has been shown in controlled clinical trials to have efficacy that is superior to placebo, simulated ECT, and antidepressant medication therapy (196). The proportion of patients with major depressive disorder who respond to ECT is high, with 80%–90% of those treated showing improvement (197). Results of several studies indicate that ECT can be effective in over half of patients with major depressive disorder who have failed antidepressant medication therapy (198–200).

The report of the APA Task Force on Electroconvulsive Therapy identified patient populations for whom ECT may be particularly beneficial and indicated (72, 201). ECT should be considered as the treatment choice for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, or food refusal leading to nutritional compromise, as well as in other situations (such as pregnancy or when a particularly rapid antidepressant response is required). ECT 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. It should be considered for all patients with functional impairment whose illness has not responded to medication or who have a medical condition that precludes the use of an antidepressant medication.

b) Side effects

ECT is generally a very safe treatment. However, although risks of morbidity and mortality in general do not exceed those associated with anesthesia alone, some types of serious medical conditions may have an increased risk with ECT as well as with other treatment modalities (72, 202–204). The chief side effects of ECT are cognitive. Treatment is associated with a transient postictal

confusional state and with a longer period of anterograde and retrograde memory interference. The anterograde memory impairment, which has been difficult to disentangle from the memory deficits accompanying major depressive disorder itself, typically resolves in a few weeks after cessation of treatment (205). Some degree of retrograde amnesia, particularly for recent memories, may continue, at least for patients receiving bilateral ECT (72, 206–209). Rarely, patients report more pervasive and persistent cognitive disruption, the basis of which is uncertain (210).

ECT may have cardiovascular side effects, mediated by changes on the autonomic nervous system. ECT can cause a transient rise in heart rate, cardiac workload, and blood pressure, which may have deleterious effects on patients with cardiovascular disease, including recent myocardial infarction, congestive heart failure, and cardiac arrhythmias (211). The presence of significant cardiovascular disease in candidates for ECT is an indication for caution and general medical or cardiology consultation.

ECT has also been associated with a transient rise in intracranial pressure and blood-brain barrier permeability (212). For these reasons, patients with evidence of increased intracranial pressure or cerebrovascular fragility are at substantially greater risk and should only receive ECT after careful general medical, neurological, or neurosurgical evaluation (72, 78).

c) Implementation

The evaluation preceding ECT should consist of a psychiatric history and examination to verify the indication for this treatment, a general medical evaluation to define risk factors (including medical history and physical examination with cognitive assessment, vital signs, and any specifically indicated laboratory tests), anesthesia evaluation addressing the nature and extent of anesthetic risk and the need for modification of medications or anesthetic technique, the obtaining of informed consent, and, finally, an evaluation that summarizes treatment indications and risks and suggests any indicated additional evaluative procedures, alterations in treatment, or modifications in ECT technique (72). In assessing cases with indications for caution (e.g., recent myocardial infarction, cardiac arrhythmias, and intracranial-space-occupying lesions), the relative risks and benefits should be carefully weighed in collaboration with an anesthesiologist and a general medical physician, cardiologist, or neurologist, as the case requires.

ECT may be administered either bilaterally or unilaterally. Compared to bilateral treatment, unilateral placement induces less cognitive interference in most patients, but in some cases it is also less effective (213). When unilateral treatment is used, stimuli that are only marginally above seizure threshold exhibit a less satisfactory antidepressant medication effect than those of higher intensity, although this effect must be balanced against the cognitive interference evoked by grossly suprathreshold stimulation. In the event that unilateral treatment is initiated and the patient does not respond satisfactorily to the initial six treatments, bilateral treatment should be considered. Stimulus parameters vary from patient to patient but should be titrated to induce an adequate generalized seizure, which is typically at least 15–25 seconds in duration (72, 214, 215).

The total course of treatment should be such that maximal remission of symptoms is achieved (i.e., the patient fully recovers or reaches a plateau); typically this involves 6 to 12 treatments and generally does not exceed 20 treatments (72, 216). ECT is typically administered every other day; less frequent administration has been associated with less cognitive impairment but also a prolonged period until onset of action (217).

Patients should be maintained on antidepressant medication therapy or lithium following acute response to ECT (218). Patients who do not respond to such maintenance medication therapies may require maintenance ECT treatment (219).

4. Light therapy

Although several trials conducted during the 1980s demonstrated that bright light therapy was more effective than a dim-light control condition, some questions have been raised concerning the adequacy of the study designs (220). However, recent trials with more adequate control

conditions have also demonstrated the effectiveness of bright light therapy over nonlight control conditions (221–223). On the basis of limited trial data, bright light therapy has been suggested as a first-line treatment in subsyndromal winter "blues" and as an adjunct in chronic major depressive disorder or dysthymia with seasonal exacerbations. Patients with a history of reactivity to ambient light, hypersomnia, atypical negative symptoms, and overeating of sweet food in the afternoon have also been considered candidates for favorable response to light treatment. On the other hand, studies of the role of light therapy in premenstrual dysphoria or in older patients with nonseasonal major depressive disorder with advanced sleep phase disorder yielded equivocal results.

Side effects of light therapy include headache, eye strain, irritability, insomnia, and occasionally hypomania, which declines by decrease of exposure time and/or distance to light. Although patients with retinal diseases or ordinary photosensitivity, systemic lupus erythematosus, and history of skin cancer are vulnerable, none of these conditions is an absolute contraindication for light therapy. Each condition would require the attention and consultative supervision of the appropriate specialist if the light therapy is to be conducted.

A 10,000-lux intensity light box slanted toward the patient's face for 30 minutes/day either once or in two divided times is the preferred short-term treatment procedure. Timing may be designed to secure adherence. The late-night application is discouraged as it may cause insomnia. Duration of treatment is titrated according to the patient's reaction. Patients usually show improvement within 1 week, but at times the full response manifests over several weeks.

Patients who are responsive may be given light therapy at each episode of recurrence, presumably without any diminished efficacy. Prophylactic use of light therapy administered in the late fall and early winter is being explored. Combining light therapy with an antidepressant medication may potentiate the effectiveness of each agent. Such an approach may be useful if either or both therapies cannot be used in full therapeutic doses. The potential photosensitizing effect of antidepressant medications should be considered, and patients receiving both treatments should be advised to take appropriate precautions.

5. St. John's wort

St. John's wort is a whole plant product with antidepressant medication properties. Since it is not regulated as a drug by the FDA, preparations lack standardization regarding their contained ingredients and composition as well as potency.

A recent review of 14 short-term, double-blind (although the distinctive taste of St. John's wort extract may have caused some unblinding) trials conducted in outpatients with mild to moderate major depressive disorder symptoms demonstrated that St. John's wort had efficacy superior to placebo and generally comparable to low-dose tricyclic treatment (e.g., amitriptyline, 30–150 mg/day) (1). The proportion experiencing any side effect was lower among those taking St. John's wort than tricyclics (25% versus 40%) (1).

Although the doses of St. John's wort used in trials ranged between 300 and 1,800 mg/day, differences in extract preparations make dose comparisons and the identification of optimal doses difficult. The combined use of St. John's wort with MAOIs is contraindicated. The safety and efficacy of the combined use of St. John's wort with other antidepressant medications is not known.

B. ACUTE PHASE PSYCHOSOCIAL INTERVENTIONS

1. Goals

A range of psychosocial interventions may be useful in the acute treatment of major depressive disorder. Although various therapeutic approaches are discussed here and in the literature as

distinct entities, such separate categorizations are primarily useful for heuristic or research purposes. In practice, psychiatrists use a combination or synthesis of various approaches and strategies; these in turn are determined by and individually tailored to each patient on the basis of that person's particular conditions and coping capacities. In actual application the techniques and the therapist-patient relationship are powerfully intertwined.

2. Efficacy

Evaluating the efficacy of psychotherapeutic approaches for major depressive disorder can be complicated by several problems. For some types of psychotherapeutic interventions, few or no clinical trials have been conducted. Those that have been conducted have compared psychotherapy to a variety of control conditions such as waiting lists, other forms of psychotherapy, medications, placebos, or no control group, making comparisons of the observed treatment effect sizes between trials difficult. Some trials have not examined the effects of psychotherapy exclusively among patients with major depressive disorder and may not have examined or adequately assessed, specifically, improvement in major depressive disorder as an outcome. In other trials, the nature of the psychotherapeutic intervention has involved a poor protocol or has been poorly described, thereby making generalization of the study results to psychotherapeutic approaches used in practice difficult.

a) Cognitive behavioral therapy

Cognitive behavioral therapy (also considered to include cognitive psychotherapy) maintains that irrational beliefs and distorted attitudes toward the self, the environment, and the future perpetuate depressive affects. The goal of cognitive behavioral therapy is to reduce depressive symptoms by challenging and reversing these beliefs and attitudes (224).

In the two decades since it was first evaluated as a treatment for major depressive disorder, cognitive behavioral therapy has been extensively studied in over 80 controlled trials. Based on different subsets of these trials, several meta-analytic studies have quantified the efficacy of cognitive behavioral therapy. Effect sizes for cognitive behavioral therapy compared to no treatment or minimal treatment have been fairly robust (generally near or above 1 standard deviation in the outcome measure) (53, 225–228). However, estimates from meta-analyses of the effectiveness of cognitive behavioral therapy relative to other treatments have been more inconsistent, probably because of differences in the criteria that were used to include or exclude trials (e.g., characteristics of study populations, interventions or control conditions, or outcome measures used). For example, some meta-analyses have concluded that effect sizes for cognitive behavioral therapy are larger than for pharmacotherapy (225–231), whereas others suggest they are equally effective (232). Effect sizes for cognitive behavioral therapy have generally been at least as large as, and in some cases larger than, for other forms of psychotherapy such as behavior therapy, interpersonal therapy, or brief dynamic psychotherapy (231).

There have been suggestions on the basis of individual clinical trials that the efficacy of cognitive behavioral therapy may differ on the basis of the severity of major depressive disorder. In subanalyses of the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program study, cognitive behavioral therapy was observed to be less effective than imipramine plus clinical management among individuals with severe depression (defined as scores $\geq$20 on the Hamilton Rating Scale for Depression or $\leq$50 on the Global Assessment of Functioning); there was also a trend for cognitive behavioral therapy to be less effective than interpersonal therapy (233). No differences were observed between cognitive behavioral therapy, interpersonal therapy, imipramine plus clinical management, or placebo plus clinical management among less severely depressed subjects. Other trials have failed to show differential responses to treatments on the basis of initial symptom severity, possibly because of lack of statistical power (230, 234).

Several studies have used clinical trial data to identify other characteristics of patients that may be associated with differential response to cognitive behavioral therapy. Factors suggested as being associated with poor response to cognitive behavioral therapy include unemployment, male gender, comorbidity, dysfunctional attitudes, and several laboratory test values (e.g., abnormal sleep EEG results, increased hypothalamic-pituitary-adrenocortical activity, and increased T_4; 235–238). On the other hand, results from several analyses have suggested that cognitive behavioral therapy may be more effective than other treatments for depressed individuals with personality disorders (42, 239).

b) Behavior therapy

Behavior therapy of major depressive disorder is based on theoretical models drawn from behavior theory (240) and social learning theory (241). Specific behavior therapy techniques include activity scheduling (155, 242), self-control therapy (243), social skills training (244), and problem solving (245).

Although the efficacy of behavior therapy has been examined in a substantial number of trials, relatively few have employed random assignments and adequate control arms. Two meta-analyses that covered 10 of these trials have concluded that behavior therapy is superior to wait listing (observed in seven of eight trials) (92, 231). Results of individual clinical trials have suggested that behavior therapy may be superior in efficacy to brief dynamic psychotherapy (246, 247) and generally comparable in efficacy to cognitive therapy (248–251) or pharmacotherapy (252).

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 (253), whereas other studies have not (254–256). Among depressed adolescents, parental involvement has been found to predict response to behavior therapy (257).

c) Interpersonal therapy

Interpersonal therapy focuses on losses, role disputes and transitions, social isolation, deficits in social skills, and other interpersonal factors that may impact the development of depression (258). Interpersonal therapy attempts to intervene by facilitating mourning and promoting recognition of related affects, resolving role disputes and transitions, and overcoming deficits in social skills to permit the acquisition of social supports.

In one trial conducted among depressed psychiatric patients, interpersonal therapy was found to be superior to nonscheduled controls and comparable to other active treatments, including cognitive therapy or antidepressant medication (231). In the NIMH Treatment of Depression Collaborative Research Program study, interpersonal therapy was also reported to be more effective than placebo plus clinical management and comparable to cognitive behavioral therapy or imipramine plus clinical management (42). However, in subanalyses, interpersonal therapy, cognitive behavioral therapy, and imipramine plus clinical management were no different from placebo plus clinical management among those with mild depression severity (defined as scores of <20 on the Hamilton depression rating scale or >50 on the Global Assessment of Functioning); among those with more severe major depressive disorder, both interpersonal therapy and imipramine plus clinical management were more effective than either cognitive behavioral therapy or placebo plus clinical management (233, 259). A controlled trial of interpersonal therapy has also been conducted demonstrating the effectiveness of interpersonal therapy among depressed primary care patients (260). After 8 months, the proportions of patients treated with interpersonal therapy, nortriptyline, or usual care that achieved remission were 46%, 48%, and 18%, respectively.

Some recent studies have also suggested possible subgroups in whom interpersonal therapy may show differential efficacy. In one trial conducted among HIV-positive patients with major depressive disorder, significantly greater improvement was observed following interpersonal therapy than supportive therapy (261). In a subsequent study among depressed HIV-positive

patients, greater improvements were observed after interpersonal therapy or interpersonal therapy plus imipramine than supportive psychotherapy or cognitive behavioral therapy (262). On the other hand, post hoc analyses of clinical trial data suggest that there may be an interaction between type of psychotherapy and dimensions of personality. Two such analyses have found that patients with major depressive disorder with personality disorders, particularly avoidant personality pathology, may be less responsive to interpersonal therapy than cognitive therapy (42, 263). Conversely, interpersonal therapy has been proposed to be more effective than cognitive therapy for patients with major depressive disorder with obsessive personality traits and for patients who are single and noncohabitating (264).

d) Psychodynamic psychotherapy

The term "psychodynamic psychotherapy" encompasses a number of psychotherapeutic interventions that may be brief or long-term in duration (265–267). These interventions share a basis in psychodynamic theories regarding the etiologic nature of psychological vulnerability, personality development, and symptom formation as shaped by developmental deficit and conflict occurring during the life cycle from earliest childhood forward (268–272). Some of these theories focus predominantly on conflicts related to guilt, shame, interpersonal relationships, the management of anxiety, and repressed or unacceptable impulses. Others are more focused on developmental psychological deficits produced by inadequacies or problems in the relationship between the child and emotional caretakers, resulting in problems of self-esteem, a sense of psychological cohesiveness, and emotional self-regulation (271, 273–277).

Psychodynamic psychotherapy is most often of longer-term duration than other psychotherapies and is usually associated with goals beyond that of immediate symptom relief. These goals are usually associated with an attempt to modify the underlying psychological conflicts and deficits that increase the patient's vulnerability to major depressive affect and the development of major depressive disorder. Psychodynamic psychotherapy is therefore much 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. It is often combined with psychopharmacologic intervention to reduce the major depressive disorder episode, which is consistent with the common belief that major depressive disorder is a biopsychosocial phenomenon. Sometimes a goal of psychodynamic psychotherapy, brief or extended, may be to help the patient accept or adhere to necessary pharmacotherapy (8).

Determining the efficacy of psychodynamic psychotherapy as a single modality in the treatment of major depressive disorder is complicated by two problems. First, many trials of psychodynamic psychotherapy for depression have included patients with conditions that would not meet DSM-IV criteria for major depressive disorder. Second, variations of psychodynamic psychotherapy have served in many studies as a nonspecific comparison treatment to other psychotherapeutic interventions; as a result, details of the psychodynamic psychotherapy employed have been poorly defined. Results of two meta-analyses suggest that brief psychodynamic psychotherapy for the treatment of major depressive disorder is more effective than a waiting list control condition but probably less effective than other forms of psychotherapy (92, 231). In one of these meta-analyses involving six trials (92), the proportions of patients considered to be responders to brief psychodynamic psychotherapy, cognitive therapy, interpersonal therapy, and behavioral therapy were 35%, 47%, 52%, and 55%, respectively. Research on the efficacy of combined pharmacotherapy and brief psychodynamic psychotherapy (278, 279) is also limited and inconclusive.

Although psychodynamic psychotherapy appears to be used widely in clinical practice, the efficacy of long-term psychodynamic psychotherapy in the acute phase of major depressive disorder has not been adequately studied in controlled trials.

e) Marital therapy and family therapy

Marital and family problems are common in the course of mood disorders, and comprehensive treatment often demands that these problems be assessed and addressed. Marital and family problems may be a consequence of major depressive disorder but may also increase vulnerability to major depressive disorder and in some instances retard recovery (280, 281). Techniques for using marital/family approaches for the treatment of major depressive disorder have been developed, including behavioral approaches (280), a psychoeducational approach, and a strategic marital therapy approach (9). Family therapy has also been used in the inpatient treatment of patients with major depressive disorder (282).

Studies of the efficacy of marital or family therapy, either as a primary or adjunctive treatment, have been conducted among patients with depressive symptoms and not among patients with, specifically, major depressive disorder. Based on data from 17 clinical trials of marital therapy, two reviews have concluded that it is an effective means for reducing major depressive disorder symptoms and risk of relapse (283, 284). Results from individual studies suggest that the efficacy of marital therapy and its effectiveness relative to other psychotherapies 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 cognitive therapy (88% versus 71%); on the other hand, among depressed subjects without marital distress, a greater proportion responded to cognitive therapy than marital therapy (85% versus 55%) (285). In another study conducted among depressed subjects with marital discord, marital therapy and cognitive behavioral therapy were both equally effective and more effective than a wait list condition (286).

f) Group therapy

Specific types of psychotherapy for which there are some data to support that they may be effective in the treatment of depression when administered in a group format include cognitive behavioral therapy (287–289) and interpersonal therapy (290–291). Although there have been meta-analyses of the relative effectiveness of psychotherapeutic approaches conducted in a group format versus an individual format, these have not specifically involved studies of patients with rigorously defined major depressive disorder (292–295).

On the basis of very limited controlled studies, supportive group therapy has also been suggested to be useful in the treatment of major depressive disorder. For example, one recent study conducted among depressed outpatients found that a mutual support group and cognitive behavioral therapy in a group format were equally effective in reducing depressive symptoms among depressed outpatients (287). In another study of patients with mild to moderate major depressive disorder who were also HIV positive, treatment with structured supportive group therapy plus placebo yielded similar decreases in depressive symptoms as structured group therapy plus fluoxetine (296). Individuals experiencing bereavement or such common stressors as chronic illness may particularly benefit from the example of others who have successfully dealt with the same or similar challenges. Survivors are offered the opportunity to gain enhanced self-esteem by making themselves models for others, and they offer newer patients successful role models.

Medication maintenance support groups may also offer benefits, although data from controlled trials among patients with major depressive disorder are lacking. Such groups provide information to the patient and to family members regarding prognosis and medication issues, thereby providing a psychoeducational forum that makes a chronic mental illness understandable in the context of a medical model.

The efficacy of self-help groups led by lay members (297) in the treatment of major depressive disorder has not been well studied. However, one recent investigation of group therapies found that a higher proportion of depressed outpatients had remitted following treatment in groups led by professionals than in groups led by nonprofessionals (287). The possibility that self-help support groups comprising individuals with major depressive disorder may serve a

useful role by enhancing the support network and self-esteem of participating patients and their families requires future study.

3. Side effects

In general, psychotherapeutic treatments are relatively safe and well-tolerated interventions. Psychotherapeutic approaches that may employ exposure to unpleasant situations (e.g., behavior therapy, cognitive behavioral therapy) may initially increase distress in patients. Psychotherapy that requires considerable time or patience to practice frequent exercises may be poorly tolerated.

One imperfect 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). In the NIMH Treatment of Depression Collaborative Research Program, dropout rates during 16 weeks of treatment with interpersonal therapy, cognitive behavioral therapy, imipramine plus clinical management, or placebo plus clinical management were 23%, 32%, 33%, and 40%, respectively (259).

4. Implementation

There can be a variety of methods for conducting psychotherapeutic interventions, both between and within specific types of psychotherapy.

Clinical considerations and other patient factors should be considered in determinations of the nature and intensity of psychosocial interventions. Generally, dynamic psychotherapy is conducted in a less directive manner than behavioral psychotherapy; transference considerations and the patient's freedom to associate into unexpected material are taken into account. More behaviorally oriented psychotherapy, on the other hand, may be conducted in a more structured manner and require patients to be instructed in practice exercises and monitoring techniques.

There are little data available on optimal length of psychosocial interventions. In many trials, cognitive behavioral therapy has been delivered in approximately 12 weekly sessions and interpersonal therapy has been delivered in 16–20 weekly sessions. In a subanalysis of one clinical trial, cognitive behavioral therapy delivered in 16 weeks was more effective than cognitive behavioral therapy delivered in 8 weeks among those with severe major depressive disorder (298).

C. PSYCHOTHERAPY COMBINED WITH PHARMACOTHERAPY

Several reviews of trials of the combination of psychotherapy and pharmacotherapy for patients with mild to moderate major depressive disorder have failed to find the combination to be superior to either treatment modality alone (92, 299). On the other hand, among patients with severe or recurrent major depressive disorder, the combination of psychotherapy (including interpersonal therapy, cognitive behavioral therapy, behavior therapy, or brief dynamic therapy) and pharmacotherapy has been found to be superior to treatment with a single modality in individual studies (38, 300–304) and a meta-analysis (305).

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 cognitive behavioral therapy may be an effective strategy for preventing relapse (306–309).

D. CONTINUATION TREATMENT

The continuation phase of treatment is generally considered to be the 16–20 weeks after achieving full remission. The goal of continuation treatment is to prevent relapse in the vulner-

able period immediately following symptomatic recovery. Several studies have shown that if antidepressant medications are discontinued following recovery, approximately 25% of patients will relapse within 2 months (92, 310, 311). There is evidence that patients who do not completely recover during acute treatment have a significantly higher risk of relapse than those who have no residual symptoms and are especially in need of treatment in later phases (312).

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 (1, 313, 314).

There is some evidence that patients who are given cognitive behavioral therapy in the acute phase have a lower rate of relapse than those who receive and then discontinue antidepressant medications in the acute phase and an equivalent relapse rate to those who take antidepressant medication in the continuation phase (234). There have also been a few recent studies of 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 (315). Results from a series of studies (307, 309, 316) suggest that cognitive behavioral therapy may be an effective continuation treatment following antidepressant medication therapy for preventing relapse (306).

When treatments are ultimately tapered and discontinued after the continuation phase, patients should be carefully monitored during and immediately after discontinuation to ensure that remission is stable. Patients who have had multiple prior episodes of major depressive disorder should be considered for maintenance medication treatment.

E. MAINTENANCE TREATMENT

Major depressive disorder is, for many, a recurrent disorder. Among those suffering from an episode of major depressive disorder, between 50% and 85% will go on to have at least one lifetime recurrence, usually within 2 or 3 years (310). Factors that have been found to be associated with a higher risk of recurrence appear in Table 2. Factors that have been found to be associated with increased severity of subsequent episodes include a history of a prior episode complicated by serious suicide attempts, psychotic features, or severe functional impairment.

Among the therapeutic options available for maintenance treatment, antidepressant medications have received the most study. There have been over 20 trials of pharmacotherapy in the maintenance phase, and results from these have generally demonstrated the effectiveness of antidepressant medication for relapse prevention (317); these trials have mainly been of tricyclic antidepressant medications (318, 319), although six trials involved newer antidepressant medications (1). Information to assist in the full range of clinical decisions regarding medication use in the maintenance phase is more limited. Results from one study suggest that full doses are superior to lower doses in the maintenance phase, despite the fact that lower doses are less likely to produce side effects (320).

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 (228). Another report suggests that interpersonal psychotherapy during the maintenance phase may be effective in lengthening the interepisode interval in some less severely ill patients not receiving medication (318).

The combined use of psychotherapy, such as cognitive behavioral therapy, cognitive therapy, or interpersonal therapy, and pharmacotherapy in the maintenance phase has also been considered by investigators, and some results suggest that the combination of antidepressant medica-

tions plus psychotherapy may be additionally effective in preventing relapse over treatment with single modalities (307, 318, 319, 321, 322).

ECT has also been used in the maintenance phase, although evidence for its benefits comes largely from case reports (197, 219, 323, 324). The optimal frequency and duration of maintenance phase ECT treatments has not been well studied.

The timing and method of discontinuing maintenance treatment has not been systematically studied. However, the risk of cholinergic rebound observed with abrupt discontinuation of some antidepressant medications together with concerns about major depressive disorder recurrences after the discontinuation of any antidepressant medication argue in favor of gradual tapering (325).

PART C: FUTURE RESEARCH NEEDS

Notable progress has been made in our understanding of major depressive disorder and its treatment, including the introduction of a variety of therapeutic agents and treatment modalities. However, many issues remain regarding how to optimally use these treatments to achieve the best health outcomes for patients with major depressive disorder. The following are a few of the types of research questions that require future study.

VI. ANTIDEPRESSANT MEDICATIONS

In terms of the use of antidepressant medications during the acute, continuation, and maintenance phases of treatment, many important questions remain.

1. What are the specific clinical indications for the use of particular antidepressant medications?
2. What are the relative efficacies of different antidepressant medications?
3. What are the relationships between antidepressant blood levels and response?
4. What are the relative risks of toxicities (e.g., cardiotoxicity) and adverse effects for different antidepressant medications?
5. What should the duration of treatment be before a patient is considered medication-resistant, and does this duration vary among agents?
6. Does the combination of antidepressants from different pharmacologic classes (e.g., SSRIs and tricyclic antidepressants) offer greater efficacy than administration of single agents?
7. What are the comparative efficacies of different antidepressant medications in the continuation and maintenance phases?
8. What are the long-term side effects of chronic use of specific antidepressant medications?
9. What is the required duration of maintenance treatment with antidepressants?
10. What are indications for a trial of discontinuation of maintenance treatment?

VII. PSYCHOTHERAPY

Many issues concerning the use of psychotherapy in the treatment of major depressive disorder during the acute, continuation, and maintenance phases also require clarification. The disparity between the widespread use of psychodynamic psychotherapy in practice and the complete lack of rigorous studies of its efficacy must be addressed. In particular, there is a critical need to design and implement rigorous, controlled studies to evaluate the efficacy and effectiveness of psychodynamic psychotherapy for the treatment of patients with major depressive disorder.

In addition, the following are critical issues:

1. What are the relative efficacies of different psychotherapeutic approaches in the acute phase of treatment?
2. What components or aspects of specific psychotherapeutic approaches are responsible for efficacy? What common elements of all effective psychotherapeutic approaches are responsible for efficacy?
3. What are the indications (e.g., subtypes of depressive disorders) for use of various forms of psychotherapy?
4. What are the efficacies of particular psychotherapeutic approaches in the continuation and maintenance phases of treatment?
5. Is the use of multiple forms of psychotherapy, either concurrently or sequentially, effective?
6. What are the optimal frequencies of psychotherapeutic contact for the various forms of psychotherapy in the acute, continuation, and maintenance phases?

VIII. ELECTROCONVULSIVE THERAPY

Regarding ECT, additional research is needed to clarify several important issues.

1. What are indications for initial treatment with bilateral electrode placement?
2. After how many unilateral treatments without satisfactory response should a switch from unilateral to bilateral electrode placement be made?
3. Can the efficacy or tolerability of ECT be increased with adjunctive antidepressant and antipsychotic agents?
4. What are the indications and best methods for providing maintenance ECT?

IX. OTHER TREATMENT MODALITIES

In addition to research on the treatments covered above, additional rigorous investigation is needed to answer questions concerning other therapeutic modalities.

1. What are the indications, relative efficacies, and safety of specific treatments such as lithium or thyroid hormone as adjuncts to antidepressant medications for nonresponders?
2. Is light therapy effective as an adjunct in nonseasonal major depressive disorder or as a primary treatment for seasonal major depressive disorder in the maintenance phase?

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American Academy of Psychoanalysis
American Association of Community Psychiatrists
American College of Emergency Physicians
American Dietetic Association
American Society of Clinical Psychopharmacology, Inc.
Black Psychiatrists of America
Royal Australian & New Zealand College of Psychiatrics
Society for Adolescent Medicine

XI. REFERENCES

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

[A] *Randomized 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.

[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 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.

1. Agency for Healthcare Policy Research: Evidence Report on Treatment of Depression—Newer Pharmacotherapies. San Antonio Evidence-Based Practice Center. Washington, DC, AHCPR, Evidence-Based Practice Centers, 1999 [F]
2. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revised). Am J Psychiatry 2002; 159(April suppl) [G]
3. American Psychiatric Association: Practice Guideline for Psychiatric Evaluation of Adults. Am J Psychiatry 1995; 152(Nov suppl):63–80 [G]
4. Lin EHB, von Korff M, Katon W, Bush T, Simon GE, Walker E, Robinson P: The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care 1995; 33:67–74 [B]
5. Thase ME, Rush AJ: Treatment-resistant depression, in Psychopharmacology: The Fourth Generation of Progress. Edited by Bloom F, Kupfer DJ. New York, Raven Press, 1995, pp 1081–1097 [F]
6. Frank E, Kupfer DJ: Axis II personality disorders and personality features in treatment-resistant and refractory depression, in Treatment Strategies for Refractory Depression. Edited by Roose SP, Glassman AH. Washington, DC, American Psychiatric Press, 1990, pp 207–221 [F]
7. Goldman W, McCulloch J, Cuffel B, Zarin DA, Suarez A, Burns BJ: Outpatient utilization patterns of integrated and split psychotherapy and pharmacotherapy for depression. Psychiatr Serv 1998; 49:477–482 [G]
8. Gray SH: Developing practice guidelines for psychoanalysis. J Psychother Pract Res 1996; 5:213–227 [F]
9. Coyne JC: Strategic therapy, in Affective Disorders and the Family: Assessment and Treatment. Edited by Clarkin JF, Haas GL, Glick JD. New York, Guilford, 1988, pp 89–113 [F]
10. Lejoyeux M, Ades J: Antidepressant discontinuation: a review of the literature. J Clin Psychiatry 1997; 58(suppl 7):11–16 [F]
11. Coupland NJ, Bell CJ, Potokar JP: Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996; 16:356–362 [D]
12. Glassman AH, Roose SP: Delusional depression. Arch Gen Psychiatry 1981; 38:424–427 [E]
13. Spiker DG, Weiss JC, Dealy RS, Griffin SJ, Hanin I, Neil JF, Perel JM, Rossi AJ, Soloff PH: The pharmacological treatment of delusional depression. Am J Psychiatry 1985; 142:430–436 [A]
14. Price LH, Conwell Y, Nelson JC: Lithium augmentation of combined neuroleptic-tricyclic treatment in delusional depression. Am J Psychiatry 1983; 140:318–322 [E]
15. Kantor SJ, Glassman AH: Delusional depression: natural history and response to treatment. Br J Psychiatry 1977; 131:351–360 [E]
16. Fink M, Taylor MA: Catatonia: a separate category for DSM-IV? Integrative Psychiatry 1991; 7:2–10 [G]
17. Liebowitz MR, Quitkin FM, Stewart JW, McGrath PJ, Harrison WM, Markowitz JS, Rabkin JG, Tricamo E, Goetz DM, Klein DF: Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988; 45:129–137 [A]
18. Davidson JR, Miller R, Turnbull CD, Sullivan JL: Atypical depression. Arch Gen Psychiatry 1982; 39:527–534 [G]

19. Quitkin FM, Harrison W, Stewart JW, McGrath PJ, Tricamo E, Ocepek-Welikson K, Rabkin JG, Wager SG, Nunes E, Klein DF: Response to phenelzine and imipramine in placebo nonresponders with atypical depression: a new application of the crossover design. Arch Gen Psychiatry 1991; 48:319–323 [A]
20. Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. Am J Psychiatry 1988; 145:306–311 [A]
21. Goodnick PJ: Acute and long-term bupropion therapy: response and side effects. Ann Clin Psychiatry 1991; 3:311–313 [C]
22. Goodnick PJ, Extein I: Bupropion and fluoxetine in depressive subtypes. Ann Clin Psychiatry 1989; 1:119–122 [C]
23. Pande AC, Birkett M, Fechner-Bates S, Haskett RF, Greden JF: Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 1996; 40:1017–1020 [A]
24. Sands BF, Ciraulo DA: Cocaine drug-drug interactions. J Clin Psychopharmacol 1992; 12:49–55 [G]
25. Grunhaus L: Clinical and psychobiological characteristics of simultaneous panic disorder and major depression. Am J Psychiatry 1988; 145:1214–1221 [F]
26. Schatzberg AF, Ballenger JC: Decisions for the clinician in the treatment of panic disorder: when to treat, which treatment to use, and how long to treat. J Clin Psychiatry 1991; 52:26–31 [G]
27. Sheehan DV, Davidson JR, Manschreck T, Van Wyck Fleet J: Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. J Clin Psychopharmacol 1983; 3:28–31 [C]
28. Clomipramine Collaborative Study Group: Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry 1991; 48:730–738 [A]
29. Jenike MA, Buttolph L, Baer L, Ricciardi J, Holland A: Open trial of fluoxetine in obsessive-compulsive disorder. Am J Psychiatry 1989; 146:909–911 [A]
30. Stoudemire A, Hill C, Gulley LR, Morris R: Neuropsychological and biomedical assessment of depression-dementia syndromes. J Neuropsychiatry Clin Neurosci 1989; 1:347–361 [C]
31. Caine ED: Pseudodementia: current concepts and future directions. Arch Gen Psychiatry 1981; 38:1359–1364 [F]
32. Akiskal HS, Rosenthal TL, Haykal RF, Lemmi H, Rosenthal RH: Characterological depressions: clinical and sleep EEG findings separating subaffective dysthymias from character spectrum disorders. Arch Gen Psychiatry 1980; 37:777–783 [B]
33. Howland RH: Pharmacotherapy of dysthymia: a review. J Clin Psychopharmacol 1991; 11:83–92 [G]
34. Keller MD, Hanks DL, Klein DN: Summary of the DSM-IV mood disorders field trial and issue overview. Psychiatr Clin North Am 1996; 19:1–28 [F]
35. Thase ME, Reynolds CF, Frank E, Simons AD: Response to cognitive-behavioral therapy in chronic depression. J Psychotherapy Practice and Research 1994; 3:204–214 [B]
36. Conte HR, Karasu TB: A review of treatment studies of minor depression 1980–1981. Am J Psychother 1992; 46:58–74 [F]
37. Frances AJ: An introduction to dysthymia. Psychiatr Annals 1993; 23:607–608 [F]
38. Keller MD, McCullough JP, Rush AJ, Klein DF, Schatzberg AF, Gelenberg J, Thase ME: Nefazodone HCI, cognitive behavioral analysis system of psychotherapy and combination therapy for the acute treatment of chronic depression, in 1999 Annual Meeting New Research Program and Abstracts. Washington, DC, American Psychiatric Association, 1999, p 178 [A]
39. Kocsis JH, Frances AJ, Voss CB, Mann JJ, Mason BJ, Sweeney J: Imipramine treatment for chronic depression. Arch Gen Psychiatry 1988; 45:253–257 [A]
40. Shea MT, Glass DR, Pilkonis PA, Watkins J, Docherty JP: Frequency and implications of personality disorders in a sample of depressed outpatients. J Personal Disord 1987; 1:27–42 [C]

41. Parsons B, Quitkin FM, McGrath PJ, Stewart JW, Tricamo E, Ocepek-Welikson K, Harrison W, Rabkin JG, Wager SG, Nunes E: Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. Psychopharmacol Bull 1989; 25:524–534 [A]
42. Shea MT, Pilkonis PA, Beckham E, Collins JF, Elkin I, Sotsky SM, Docherty JP: Personality disorders and treatment outcome in the NIMH Treatment of Depression Collaborative Research Program. Am J Psychiatry 1990; 147:711–718 [A]
43. Rosenthal NE, Sack DA, Carpenter CJ, Parry BL, Mendelson WB, Wehr TA: Antidepressant effects of light in seasonal affective disorder. Am J Psychiatry 1985; 142:163–170 [C]
44. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, APA, 1994 [G]
45. Zisook S, Shuchter SR: Depression through the first year after the death of a spouse. Am J Psychiatry 1991; 148:1346–1352 [C]
46. Escobar JI, Gomez J, Tuason VB: Depressive phenomenology in North and South American patients. Am J Psychiatry 1983; 140:47–51 [C]
47. Escobar JI, Tuason VB: Antidepressant agents: a cross-cultural study. Psychopharmacol Bull 1980; 16:49–52 [C]
48. Marcos LR, Cancro R: Psychopharmacotherapy of Hispanic depressed patients: clinical observations. Am J Psychother 1982; 36:505–512 [F]
49. Marcos LR, Uruyo L, Kesselman M, Alpert M: The language barrier in evaluating Spanish-American patients. Arch Gen Psychiatry 1973; 29:655–659 [C]
50. Nelson JC, Mazure CM, Bowers MBJ, Jatlow PI: A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991; 48:303–307 [C]
51. American Academy of Child and Adolescent Psychiatry: Practice Parameters for the Assessment and Treatment of Children and Adolescents With Depressive Disorders. Washington, DC, AACAP, 1998 [G]
52. Reynolds CF, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ: Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999; 281:39–45 [A]
53. Robinson RG, Starkstein SE: Current research in affective disorders following stroke. J Neuropsychiatry Clin Neurosci 1990; 2:1–14 [F]
54. Nelson JC, Jatlow PI, Mazure CM: Rapid desipramine dose adjustment using 24-hour levels. J Clin Psychopharmacol 1987; 7:72–77 [C]
55. Wisner KL, Gelenberg AJ, Leonard H, Zarin D, Frank E: Pharmacologic treatment of depression during pregnancy. JAMA 1999; 282:1264–1269 [F]
56. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL: Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335:1010–1015 [B]
57. Nurnberg HG: An overview of somatic treatment of psychosis during pregnancy and postpartum. Gen Hosp Psychiatry 1989; 11:328–338 [F]
58. Gitlin MJ, Pasnau RO: Psychiatric syndromes linked to reproductive function in women: a review of current knowledge. Am J Psychiatry 1989; 146:1413–1422 [F]
59. Brockington IF, Cernik KF, Schofield EM, Downing AR, Francis AF, Keelan C: Puerperal psychosis: phenomena and diagnosis. Arch Gen Psychiatry 1981; 38:829–833 [C]
60. Ananth J: Side effects in the neonate from psychotropic agents excreted through breast feeding. Am J Psychiatry 1978; 135:801–805 [E]
61. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592–606 [E]

62. Akiskal HS, Walker P, Puzantian VR, King D, Rosenthal TL, Dranon M: Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. J Affect Disord 1983; 5:115–128 [A]
63. Nelson JC, Kennedy JS, Pollock BG, Laghrissi-Thode F, Narayan M, Nobler MS, Robin DW, Gergel I, McCafferty J, Roose S: Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. Am J Psychiatry 1999; 156:1024–1028 [A]
64. Bigger JT, Giardina EG, Perel JM, Kantor SJ, Glassman AH: Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 1977; 296:206–208 [G]
65. Connolly SJ, Mitchell LB, Swerdlow CD, Mason JW, Winkle RA: Clinical efficacy and electrophysiology of imipramine for ventricular tachycardia. Am J Cardiol 1984; 53:516–521 [B]
66. Dalack GW, Roose SP, Glassman AH: Tricyclics and heart failure (letter). Am J Psychiatry 1991; 148:1601 [E]
67. Giardina EG, Barnard T, Johnson L, Saroff AL, Bigger JT, Louie M: The antiarrhythmic effect of nortriptyline in cardiac patients with ventricular premature depolarizations. J Am Coll Cardiol 1986; 7:1363–1369 [E]
68. Glassman AH, Johnson LL, Giardina EG, Walsh BT, Roose SP, Cooper TB, Bigger JT: The use of imipramine in depressed patients with congestive heart failure. JAMA 1983; 250:1997–2001 [C]
69. Roose SP, Glassman AH, Giardina EG, Walsh BT, Woodring S, Bigger JT: Tricyclic antidepressants in depressed patients with cardiac conduction disease. Arch Gen Psychiatry 1987; 44:273–275 [A]
70. Schwartz P, Wolf S: QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978; 57:1074–1077 [G]
71. Applegate RJ: Diagnosis and management of ischemic heart disease in the patient scheduled to undergo electroconvulsive therapy. Convuls Ther 1997; 13:128–144 [F]
72. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990 [G]
73. Dolinski SY, Zvara DA: Anesthetic considerations of cardiovascular risk during electroconvulsive therapy. Convuls Ther 1997; 13:157–164 [E]
74. Rayburn BK: Electroconvulsive therapy in patients with heart failure or valvular heart disease. Convuls Ther 1997; 13:145–156 [F]
75. Weiner RD, Coffey CE, Krystal AD: Electroconvulsive therapy in the medical and neurologic patient, in Psychiatric Care of the Medical Patient, 2nd ed. Edited by Stoudemire A, Fogel B, Greenberg D. New York, Oxford University Press, 1999 [F]
76. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EGV: Cardiovascular effects of bupropion in depressed patients with heart disease. Am J Psychiatry 1991; 148:512–516 [C]
77. Roose SP, Glassman AH, Giardina EG, Johnson L, Walsh BT, Bigger JT: Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. J Clin Psychopharmacol 1987; 7:247–251 [A]
78. Krystal AD, Coffey CE: Neuropsychiatric considerations in the use of electroconvulsive therapy. J Neuropsychiatry Clin Neurosci 1997; 9:283–292 [F]
79. Lieberman E, Stoudemire A: Use of tricyclic antidepressants in patients with glaucoma. Psychosomatics 1987; 28:145–148 [G]
80. Thase ME: Effects of venlafaxine on blood pressure: a meta-analysis of original data on 3744 depressed patients. J Clin Psychiatry 1998; 59:502–508 [E]
81. Goetz CG, Tanner CM, Klawans HL: Bupropion in Parkinson's disease. Neurology 1984; 34:1092–1094 [C]

82. Monoamine oxidase inhibitors for depression. Med Lett Drugs Ther 1980; 22:58–60 [G]
83. Andersen K, Balldin J, Gottfries CG, Granerus AK, Modigh K, Svennerholm L, Wallin A: A double-blind evaluation of electroconvulsive therapy in Parkinson's disease with on-off phenomena. Acta Neurol Scand 1987; 76:191–199 [A]
84. Regier DA, Boyd JH, Burke JD Jr, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ: One-month prevalence of mental disorders in the United States: based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1988; 45:977–986 [A]
85. Pincus HA, Zarin DZ, Tanielian TL, Johnson JL, West JC, Petit AR, Marcus SC, Kessler RC, McIntyre JS: Psychiatric patients and treatments in 1997: findings from the American Psychiatric Practice Research Network. Arch Gen Psychiatry 1999; 56:442–449 [C]
86. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD: Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999; 156:1000–1006 [B]
87. Klerman GL, Weissman MM: The course, morbidity and costs of depression. Arch Gen Psychiatry 1992; 49:831–834 [G]
88. Keller MD, Beardslee WR, Dorer DJ, Lavori PW, Samuelson H, Klerman GL: Impact of severity and chronicity of parental affective illness on adaptive functioning and psychopathology in children. Arch Gen Psychiatry 1986; 43:930–937 [B]
89. Mintz J, Mintz LI, Arruda MJ, Hwang SS: Treatments of depression and the functional capacity to work. Arch Gen Psychiatry 1992; 49:761–768 [E]
90. Kuhn R: The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 1958; 115:459–464 [B]
91. Brotman AW, Falk WE, Gelenberg AJ: Pharmacologic treatment of acute depressive subtypes, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987, pp 1031–1040 [F]
92. Depression Guideline Panel: Clinical Practice Guideline Number 5: Depression in Primary Care, Treatment of Major Depression: HHS Publication 93-0551. Rockville, Md, Agency for Health Care Policy and Research, 1993 [E]
93. Klein DF, Gittelman R, Quitkin FM, Rifkin A: Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children, 2nd ed. Baltimore, Williams & Wilkins, 1980 [G]
94. Klerman GL, Cole JO: Clinical pharmacology of imipramine and related antidepressant compounds. Int J Psychiatry 1967; 3:267–304 [F]
95. Potter WZ, Manji HK, Rudorfer MV: Tricyclics and tetracyclics, in American Psychiatric Press Textbook of Psychopharmacology, 2nd ed. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Press, 1998, pp 199–218 [F]
96. Coryell W, Turner R: Outcome and desipramine therapy in subtypes of non-psychotic major depression. J Affect Disord 1985; 9:149–154 [B]
97. Fairchild CJ, Rush AJ, Vasavada N, Giles DE, Khatami M: Which depressions respond to placebo? Psychiatry Res 1986; 18:217–226 [B]
98. Joyce PR, Paykel ES: Predictors of drug response in depression. Arch Gen Psychiatry 1989; 46:89–99 [F]
99. Stewart JW, Quitkin FM, Liebowitz MR, McGrath PJ, Harrison WM, Klein DF: Efficacy of desipramine in depressed outpatients: response according to Research Diagnostic Criteria diagnoses and severity of illness. Arch Gen Psychiatry 1989; 40:220–227 [A]
100. Paykel ES: Depressive typologies and response to amitriptyline. Br J Psychiatry 1972; 120:147–156 [B]
101. Raskin A, Crook TA: The endogenous-neurotic distinction as a predictor of response to antidepressant drugs. Psychol Med 1976; 6:59–70 [G]
102. Danish University Antidepressant Group: Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990; 18:289–299 [A]

103. Perry PJ: Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 1996; 39:1–6 [F]
104. Paykel ES: Treatment of depression: the relevance of research for clinical practice. Br J Psychiatry 1989; 155:754–763 [F]
105. Anderson IM, Tomenson BM: Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. Br Med J 1995; 310:1433–1438 [E]
106. Rickels K, Schweizer E: Clinical overview of serotonin reuptake inhibitors. J Clin Psychiatry 1990; 51:9–12 [F]
107. Delgado PL, Price LH, Charney DS, Heninger GR: Efficacy of fluvoxamine in treatment-refractory depression. J Affect Disord 1988; 15:55–60 [B]
108. Golden RN, Brown TM, Miller H, Evans DL: The new antidepressants. NC Med J 1988; 49:549–554 [F]
109. Schatzberg AF: Trazodone: a 5-year review of antidepressant efficacy. Psychopathology 1987; 20(suppl 1):48–56 [F]
110. Cunningham LA, Borison RL, Carman JS, Chouinard G, Crowder JE, Diamond BI, Fischer DE, Hearst E: A comparison of venlafaxine, trazodone, and placebo in major depression. J Clin Psychopharmacol 1994; 14:99–106 [A]
111. Weisler RH, Johnston JA, Lineberry CG, Samara B, Branconnier RJ, Billow AA: Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol 1994; 14:170–179 [A]
112. Klein HE, Muller N: Trazodone in endogenous depressed patients: a negative report and a critical evaluation of the pertaining literature. Prog Neuropsychopharmacol Biol Psychiatry 1985; 9:173–186 [B]
113. Shopsin B, Cassano GB, Conti L: An overview of new second generation antidepressant compounds: research and treatment implications, in Antidepressants: Neurochemical, Behavioral and Clinical Perspectives. Edited by Enna SJ, Malick J, Richelson E. New York, Raven Press, 1981, pp 219–251 [F]
114. Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico MF: A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989; 25:219–221 [A]
115. Fontaine R, Ontiveros A, Elie R, Kensler TT, Roberts DL, Kaplita S, Ecker JA, Faludi G: A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994; 55:234–241 [A]
116. Mendels J, Reimherr F, Marcus RN, Roberts DL, Francis RJ, Anton SF: A double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of depressed outpatients. J Clin Psychiatry 1995; 56(suppl 6):30–36 [A]
117. Pitts WM, Fann WE, Halaris AE, Dressler DM, Sajadi C, Snyder S, Ilaria RL: Bupropion in depression: a tri-center placebo-controlled study. J Clin Psychiatry 1983; 44(5, pt 2): 95–100 [A]
118. Chouinard G: Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983; 44:121–129 [A]
119. Davidson J, Miller R, Van Wyck Fleet J, Strickland R, Manberg P, Allen S, Parrott R: A double-blind comparison of bupropion and amitriptyline in depressed patients. J Clin Psychiatry 1983; 44:115–117 [B]
120. Feighner J, Hendrickson G, Miller L, Stern W: Double-blind comparison of doxepin vs bupropion in outpatients with major depressive disorder. J Clin Psychopharmacol 1986; 6:27–32 [A]
121. Mendels J, Amin MM, Chouinard G, Cooper AJ, Miles JE, Remick RA, Saxena B, Secunda SK, Singh AN: A comparative study of bupropion and amitriptyline in depressed outpatients. J Clin Psychiatry 1983; 44:118–120 [A]

122. Feighner JP, Gardner EA, Johnston JA, Batey SR, Khayrallah MA, Ascher JA, Lineberry CG: Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991; 52:329–335 [A]
123. Claghorn JL, Lesem MD: A double-blind placebo-controlled study of Org 3770 in depressed outpatients. J Affect Disord 1995; 34:165–171 [A]
124. Guelfi JD, White C, Hackett D, Guichoux JY, Magni G: Effectiveness of venlafaxine in patients hospitalized with major depression and melancholia. J Clin Psychiatry 1995; 56:450–458 [A]
125. Holm KJ, Markham A: Mirtazapine: a review of its use in major depression. CNS Drugs 1999; 57:607–631 [F]
126. Kasper S: Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. Int Clin Psychopharmacol 1995; 10(suppl 4):25–35; correction, 1996; 11:153 [F]
127. Schweizer E, Feighner J, Mandos LA, Rickels K: Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. J Clin Psychiatry 1994; 55:104–108 [A]
128. Zivkov M, DeJongh G: Org 3770 versus amitriptyline: a 6-week randomized, double-blind multicentre trial in hospitalized depressed patients. Human Psychopharmacology 1995; 10:173–180 [B]
129. Kelsey JE: Dose-response relationship with venlafaxine. J Clin Psychopharmacol 1996; 16 (suppl 2):21S–28S [A]
130. Montgomery SA: Reboxetine: additional benefits to depressed patients. J Psychopharmacol 1997; 11(4 suppl):S9–S15 [F]
131. Davidson J, Raft D, Pelton S: An outpatient evaluation of phenelzine and imipramine. J Clin Psychiatry 1987; 48:143–146 [B]
132. Himmelhoch JM, Thase ME, Mallinger AG, Houck P: Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991; 148:910–916 [A]
133. McGrath PJ, Stewart JW, Harrison W, Wager S, Quitkin FM: Phenelzine treatment of melancholia. J Clin Psychiatry 1986; 47:420–422 [B]
134. Quitkin FM, Rifkin A, Klein DF: Monoamine oxidase inhibitors: a review of antidepressant effectiveness. Arch Gen Psychiatry 1979; 36:749–760 [F]
135. Thase ME, Trivedi MH, Rush AJ: MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995; 12:185–219 [E]
136. White K, Razani J, Cadow B, Gelfand R, Palmer R, Simpson G, Sloane RB: Tranylcypromine vs nortriptyline vs placebo in depressed outpatients: a controlled trial. Psychopharmacology (Berl) 1984; 82:259–262 [B]
137. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF: Atypical depression, panic attacks, and response to imipramine and phenelzine: a replication. Arch Gen Psychiatry 1990; 47:935–941 [A]
138. Zisook S, Braff DL, Click MA: Monoamine oxidase inhibitors in the treatment of atypical depression. J Clin Psychopharmacol 1985; 5:131–137 [A]
139. Himmelhoch JM, Fuchs CZ, Symons BJ: A double-blind study of tranylcypromine treatment of major anergic depression. J Nerv Ment Dis 1982; 170:628–634 [A]
140. Thase ME, Mallinger AG, McKnight D, Himmelhoch JM: Treatment of imipramine-resistant recurrent depression, IV: a double-blind crossover study of tranylcypromine for anergic bipolar depression. Am J Psychiatry 1992; 149:195–198 [A]
141. Stoudemire A, Atkinson P: Use of cyclic antidepressants in patients with cardiac conduction disturbance. Gen Hosp Psychiatry 1988; 10:389–397 [G]
142. Veith RC, Raskind MA, Caldwell JH, Barnes RF, Gumbrecht G, Ritchie JL: Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. N Engl J Med 1982; 306:954–959 [A]
143. Garvey MJ, Tollefson GD: Occurrence of myoclonus in patients treated with cyclic antidepressants. Arch Gen Psychiatry 1987; 44:269–272 [E]

144. Preskorn SH, Jerkovich GS: Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. J Clin Psychopharmacol 1990; 10:88–95 [E]
145. Frazer A: Antidepressants. J Clin Psychiatry 1997; 58:9–25 [F]
146. Walker PW, Cole JO, Gardner EA, Hughes AR, Johnston JA, Batey SR, Lineberry CG: Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993; 54:459–465 [B]
147. Pollack MH, Rosenbaum JF: Management of antidepressant-induced side effects: a practical guide for the clinician. J Clin Psychiatry 1987; 48:3–8 [G]
148. Doughty MJ, Lyle WM: Medications used to prevent migraine headaches and their potential ocular adverse effects. Optom Vis Sci 1995; 72:879–891 [F]
149. Hamilton JA, Halbreich U: Special aspects of neuropsychiatric illness in women: with a focus on depression. Annu Rev Med 1993; 44:355–364 [F]
150. Gerber PE, Lynd LD: Selective serotonin-reuptake inhibitor-induced movement disorders. Ann Pharmacother 1998; 32:692–698 [E]
151. Leo RJ: Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996; 57:449–454 [E]
152. Marcus ER, Bradley SS: Combination of psychotherapy and psychopharmacotherapy with treatment-resistant inpatients with dual diagnoses. Psychiatr Clin North Am 1990; 13:209–214 [E]
153. Bouwer CD, Harvey BH: Phasic craving for carbohydrate observed with citalopram. Int Clin Psychopharmacol 1996; 11:273–278 [B]
154. Michelson D, Amsterdam JD, Quitkin FM, Reimherr F, Rosenbaum JF, Zajecka J, Sundell KL, Kim Y, Beasley CM Jr: Changes in weight during a 1-year trial of fluoxetine. Am J Psychiatry 1999; 156:1170–1176 [A]
155. Lewinsohn PM, Antonuccio DA, Steinmetz-Breckinridge J, Teri L: The Coping With Depression Course: A Psychoeducational Intervention for Unipolar Depression. Eugene, Ore, Castalia Publishing, 1984 [G]
156. Metz A, Shader RI: Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. Int Clin Psychopharmacol 1990; 5:191–194 [G]
157. Beasley CM Jr, Masica DN, Heiligenstein JH, Wheadon DE, Zerbe RL: Possible monoamine oxidase inhibitor-serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. J Clin Psychopharmacol 1993; 13:312–320 [F]
158. Vitullo RN, Wharton JM, Allen NB, Pritchett EL: Trazodone-related exercise-induced nonsustained ventricular tachycardia. Chest 1990; 98:247–248 [G]
159. Aronson MD, Hafez H: A case of trazodone-induced ventricular tachycardia. J Clin Psychiatry 1986; 47:388–389 [G]
160. Thompson JW Jr, Ware MR, Blashfield RK: Psychotropic medication and priapism: a comprehensive review. J Clin Psychiatry 1990; 51:430–433 [F]
161. Davis R, Wilde MI: Mirtazapine: a review of its pharmacology and therapeutic potential in the management of major depression. CNS Drugs 1996; 5:389–402 [F]
162. Mucci M: Reboxetine: a review of antidepressant tolerability. J Psychopharmacol 1997; 11(4 suppl):S33–S37 [F]
163. Gardner DM, Shulman KI, Walker SE, Tailor SAN: The making of a user friendly MAOI diet. J Clin Psychiatry 1996; 57:99–104 [F]
164. Schenk CH, Remick RA: Sublingual nifedipine in the treatment of hypertensive crisis associated with monoamine oxidase inhibitors (letter). Ann Emerg Med 1989; 18:114–115 [B]
165. Grossman E, Messerli FH, Grodzicki T, Kowey P: Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? JAMA 1996; 276:1328–1331 [F]
166. Sternbach H: The serotonin syndrome. Am J Psychiatry 1991; 148:705–713 [F]

167. Gelenberg AJ: Serotonin syndrome update. Biological Therapies in Psychiatry Newsletter 1997; 20:33–34 [F]
168. Beasley CM Jr, Sayler ME, Cunningham GE, Weiss AM, Masica DN: Fluoxetine in tricycylic refractory major depressive disorder. J Affect Disord 1990; 20:193–200 [B]
169. Jenner PN: Paroxetine: an overview of dosage, tolerability, and safety. Int Clin Psychopharmacol 1992; 6(suppl 4):69–80 [F]
170. Montgomery SA, Pedersen V, Tanghoj P, Rasmussen C, Rioux P: The optimal dosing regimen for citalopram—a meta-analysis of nine placebo-controlled studies. Int Clin Psychopharmacol 1994; 9(suppl 1):35–40 [E]
171. Quitkin FM, Rabkin JG, Markowitz JM, Stewart JW, McGrath PJ, Harrison W: Use of pattern analysis to identify true drug response. Arch Gen Psychiatry 1987; 44:259–264 [A]
172. Quitkin FM, Rabkin JG, Ross D, McGrath PJ: Duration of antidepressant drug treatment: what is an adequate trial? Arch Gen Psychiatry 1984; 41:238–245 [G]
173. Katz MM, Koslow SH, Maas JW, Frazer A, Bowden CL, Casper R, Croughan J, Kocsis J, Redmond E Jr: The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychol Med 1987; 17:297–309 [C]
174. Guscott R, Grof P: The clinical meaning of refractory depression: a review for the clinician. Am J Psychiatry 1991; 148:695–704 [G]
175. Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, Wilhem K: Carbamazepine for treatment-resistant melancholia. J Clin Psychiatry 1991; 52:472–476 [C]
176. Hayes SG: Long-term use of valproate in primary psychiatric disorders. J Clin Psychiatry 1989; 50:35–39 [D]
177. Rosenstein DL, Takeshita J, Nelson JC: Fluoxetine-induced elevation and prolongation of tricyclic levels in overdose (letter). Am J Psychiatry 1991; 148:807 [E]
178. Price LH, Charney DS, Heninger GR: Variability of response to lithium augmentation in refractory depression. Am J Psychiatry 1986; 143:1387–1392 [C]
179. Kramlinger KG, Post RM: The addition of lithium to carbamazepine: antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatry 1989; 46:794–800 [C]
180. Prange AJ, Loosen PT, Wilson IC, Lipton MA: The therapeutic use of hormones of the thyroid axis in depression, in The Neurobiology of Mood Disorders. Edited by Post R, Ballenger J. Baltimore, Williams & Wilkins, 1984, pp 311–322 [G]
181. Feighner JP, Herbstein J, Damlouji N: Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. J Clin Psychiatry 1985; 46:206–209 [G]
182. Wharton RN, Perel JM, Dayton PG, Malitz S: A potential clinical use for methylphenidate (Ritalin) with tricyclic antidepressants. Am J Psychiatry 1971; 127:1619–1625 [E]
183. Razani J, White KL, White J, Simpson G, Sloane RB, Rebal R, Palmer R: The safety and efficacy of combined amitriptyline and tranylcypromine antidepressant treatment: a controlled trial. Arch Gen Psychiatry 1983; 40:657–661 [A]
184. Young JPR, Lader MH, Hughes WC: Controlled trial of trimipramine, monoamine oxidase inhibitors, and combined treatment in depressed outpatients. Br Med J 1979; 2:1315–1317 [A]
185. Devlin MJ, Walsh BT: Use of monoamine oxidase inhibitors in refractory depression, in American Psychiatric Press Review of Psychiatry, vol 9. Edited by Tasman A, Goldfinger SM, Kaufmann CA. Washington, DC, American Psychiatric Press, 1990, pp 74–90 [F]
186. Prudic J, Sackeim HA: Refractory depression and electroconvulsive therapy, in Treatment Strategies for Refractory Depression. Edited by Roose SP, Glassman AH. Washington, DC, American Psychiatric Press, 1990, pp 111–128 [G]
187. El-Ganzouri A, Ivankovich AD, Braverman B, McCarthy R: Monoamine oxidase inhibitors: should they be discontinued preoperatively? Anesth Analg 1985; 64:592–596 [B]
188. Klapheke MM: Combining ECT and antipsychotic agents: benefits and risks. Convuls Ther 1993; 9:241–255 [F]
189. Klapheke MM: Electroconvulsive therapy consultation: an update. Convuls Ther 1997; 13:227–241 [F]

190. Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C, Bech P: Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. Acta Psychiatr Scand 1996; 94:241–251 [A]
191. Nelson JP, Benjamin L: Efficacy and safety of combined ECT and tricyclic antidepressant therapy in the treatment of depressed geriatric patients. Convuls Ther 1989; 5:321–329 [E]
192. Penney JF: Concurrent and close temporal administration of lithium and ECT. Convuls Ther 1990; 6:139–145 [D]
193. Hill GE, Wong KC, Hodges MR: Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. Anesthesiology 1976; 44:439–442 [E]
194. Jha AK, Stein GS, Fenwick P: Negative interaction between lithium and electroconvulsive therapy—a case control study. Br J Psychiatry 1996; 168:241–243 [D]
195. Lippman SB, Tao CA: Electroconvulsive therapy and lithium: safe and effective treatment. Convuls Ther 1993; 9:54–57 [G]
196. Janicak PG, Davis JM, Gibbons RD, Ericksen S, Chang S, Gallagher P: Efficacy of ECT: a meta-analysis. Am J Psychiatry 1985; 142:297–302 [E]
197. Weiner RD: Electroconvulsive therapy, in Treatments of Psychiatric Disorders. Edited by Gabbard GO. Washington, DC, American Psychiatric Press, 1995, pp 1237–1262 [G]
198. Devanand DP, Sackeim HA, Prudic J: Electroconvulsive therapy in the treatment-resistant patient. Psychiatr Clin North Am 1991; 14:905–923 [F]
199. Avery D, Winokur G: The efficacy of electroconvulsive therapy and antidepressants in depression. Biol Psychiatry 1977; 12:507–523 [F]
200. Paul SM, Extein I, Calil HM, Potter WZ, Chodoff P, Goodwin FK: Use of ECT with treatment-resistant depressed patients at the National Institute of Mental Health. Am J Psychiatry 1981; 138:486–489 [B]
201. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association. Washington, DC, APA, 1990 [G]
202. Abrams R: The mortality rate with ECT. Convuls Ther 1997; 13:125–127 [G]
203. Fink M: Efficacy and safety of induced seizures (ECT) in man. Compr Psychiatry 1978; 19:1–18 [F]
204. Gomez J: Subjective side-effects of ECT. Br J Psychiatry 1975; 127:609–611 [B]
205. Stoudemire A, Hill CD, Morris R, Dalton ST: Improvement in depression-related cognitive dysfunction following ECT. J Neuropsychiatry Clin Neurosci 1995; 7:31–34 [B]
206. McElhiney MC, Moody BJ, Steif BL, Prudic J, Devanand DP, Nobler MS, Sackeim HA: Autobiographical memory and mood: effects of electroconvulsive therapy. Neuropsychology 1995; 9:501–517 [A]
207. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC: Predictors of retrograde amnesia following ECT. Am J Psychiatry 1995; 152:995–1001 [A]
208. Squire LR, Slater PC, Miller PL: Retrograde amnesia and bilateral electroconvulsive therapy: long-term follow-up. Arch Gen Psychiatry 1981; 38:89–95 [C]
209. Weiner RD, Rogers HJ, Davidson JR, Squire LR: Effects of stimulus parameters on cognitive side effects. Ann NY Acad Sci 1986; 462:315–325 [B]
210. Squire LR, Slater PC: Electroconvulsive therapy and complaints of memory dysfunction: a prospective three-year follow-up study. Br J Psychiatry 1983; 142:1–8 [B]
211. Dec GW Jr, Stern TA, Welch C: The efforts of electroconvulsive therapy on serial electrocardiograms and serum cardiac enzyme values: a prospective study of depressed hospitalized inpatients. JAMA 1985; 253:2525–2529 [B]
212. Abrams R: Electroconvulsive Therapy, 3rd ed. New York, Oxford University Press, 1997 [G]
213. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM: Effects of stimulus intensity and electrode placement

on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 1993; 328:839–846 [A]
214. Krystal AD, Weiner RD: ECT seizure therapeutic adequacy. Convuls Ther 1994; 10:153–164 [F]
215. Weiner RD, Coffey CE, Krystal AD: The monitoring and management of electrically induced seizures. Psychiatr Clin North Am 1991; 14:845–869 [F]
216. Hales RE, Yudofsky SC, Talbott JA (eds): The American Psychiatric Press Textbook of Psychiatry, 3rd ed. Washington, DC, American Psychiatric Press, 1999 [G]
217. Lerer B, Shapira B, Calev A, Tubi N, Drexler H, Kindler S, Lidsky D, Schwartz JE: Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. Am J Psychiatry 1995; 152:564–570 [A]
218. Shapira B, Gorfine M, Lerer B: A prospective study of lithium continuation therapy in depressed patients who have responded to electroconvulsive therapy. Convuls Ther 1995; 11:80–85 [B]
219. Schwarz T, Loewenstein J, Isenberg KE: Maintenance ECT: indications and outcome. Convuls Ther 1995; 11:14–23 [B]
220. Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B: Light therapy for seasonal affective disorder: a review of efficacy. Neuropsychopharmacology 1989; 2:1–22 [B]
221. Eastman CI, Young MA, Fogg LF, Liu L, Meaden PM: Bright light treatment of winter depression: a placebo-controlled trial. Arch Gen Psychiatry 1998; 55:883–889 [B]
222. Terman M, Terman JS, Ross DC: A controlled trial of timed bright light and negative air ionization for treatment of winter depression. Arch Gen Psychiatry 1998; 55:875–882 [B]
223. Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, Blood ML, Jackson JM: Morning versus evening light treatment of patients with winter depression. Arch Gen Psychiatry 1998; 55:890–896 [B]
224. Beck AT, Rush AJ, Shaw BF, Emery G: Cognitive Therapy of Depression. New York, Guilford, 1979 [G]
225. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM: A meta-analysis of the effects of cognitive therapy in depressed patients. J Affect Disord 1998; 49:59–72 [E]
226. Dobson KS: A meta-analysis of the efficacy of cognitive therapy for depression. J Consult Clin Psychol 1989; 57:414–419 [E]
227. Gaffan EA, Tsaousis I, Kemp-Wheeler SM: Researcher allegiance and meta-analysis: the case of cognitive therapy for depression. J Consult Clin Psychol 1995; 63:966–980 [E]
228. Blackburn IM, Moore RG: Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. Br J Psychiatry 1997; 171:328–334 [B]
229. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD: Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. Am J Psychiatry 1999; 156:1007–1013 [E]
230. Hollon SD, DeRubeis RJ, Evans MD, Wierner MJ, Garvey MJ, Grove WM, Tuason VB: Cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 1992; 49:774–781 [A]
231. Jarrett RB, Rush AJ: Short-term psychotherapy of depressive disorders: current status and future directions. Psychiatry 1994; 57:115–132 [F]
232. Clark DM, Salkovskis PM, Hackmann A, Middleton H, Anastasiades P, Gelder M: A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry 1994; 164:759–769 [B]
233. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP: National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989; 46:971–982 [F]

234. Evans MD, Hollong SD, Garvey MJ, Piasecki JM, Grove WM, Garvey MJ, Tuason VB: Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 1992; 49:802–808 [B]
235. Joffe R, Segal Z, Singer W: Change in thyroid hormone levels following response to cognitive therapy for major depression. Am J Psychiatry 1996; 153:411–413 [B]
236. Thase ME, Dubé S, Bowler K, Howland RH, Myers JE, Friedman E, Jarrett DB: Hypothalamic-pituitary-adrenocortical activity and response to cognitive behavior therapy in unmedicated, hospitalized depressed patients. Am J Psychiatry 1996; 153:886–891 [B]
237. Thase ME, Simons AD, Reynolds CF: Abnormal electroencephalographic sleep profiles in major depression: association with response to cognitive behavior therapy. Arch Gen Psychiatry 1996; 53:99–108 [B]
238. Blatt SJ, Quinlan DM, Zuroff DC, Pilkonis PA: Interpersonal factors in brief treatment of depression: further analyses of the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1996; 64:162–171 [F]
239. Patience DA, McGuire RJ, Scott AI, Freeman CP: The Edinburgh Primary Care Depression Study: personality disorders and outcome. Br J Psychiatry 1995; 167:324–330
240. Ferster CB: A functional analysis of depression. Am Psychol 1973; 10:857–870 [F]
241. Bandura A: Social Learning Theory. Englewood Cliffs, NJ, Prentice-Hall, 1977 [G]
242. Lewinsohn PM, Clarke G: Group treatment of depressed individuals: the Coping With Depression Course. Advances in Behavioral Research and Therapy 1984; 6:99–114 [F]
243. Rehm LP: Behavior Therapy for Depression. New York, Academic Press, 1979 [G]
244. Bellack AS, Hersen M: A comparison of social-skills training, pharmacotherapy and psychotherapy for depression. Behav Res Ther 1983; 21:101–107 [A]
245. Nezu AM: Efficacy of a social problem-solving therapy for unipolar depression. J Consult Clin Psychol 1986; 54:196–202 [A]
246. McLean PD, Hakstian AR: Clinical depression: comparative efficacies of outpatient treatments. J Consult Clin Psychol 1979; 47:818–836 [F]
247. Steuer JL, Mintz J, Hammen CL, Hill MA, Jarvik LF, McCarley T, Motoike P, Rosen R: Cognitive-behavioral and psychodynamic group psychotherapy in treatment of geriatric depression. J Consult Clin Psychol 1984; 52:180–189 [B]
248. Beach SR, O'Leary KD: Extramarital sex: impact on depression and commitment in couples seeking marital therapy. J Sex Marital Ther 1985; 11:99–108 [D]
249. Jacobson NS, Dobson K, Fruzetti AE, Schmaling KB, Salusky S: Marital therapy as a treatment for depression. J Consult Clin Psychol 1991; 59:547–557 [G]
250. Rabin AS, Kaslow NJ, Rehm LP: Factors influencing continuation in a behavioral therapy. Behav Res Ther 1985; 23:695–698 [C]
251. Thompson JK, Williams DE: An interpersonally based cognitive-behavioral psychotherapy. Prog Behav Modif 1987; 21:230–258 [G]
252. Miller IW, Norman WH, Keitner GI, Bishop SB: Cognitive-behavioral treatment of depressed inpatients. Behavior Therapy 1989; 20:25–47 [B]
253. Taylor S, McLean P: Outcome profiles in the treatment of unipolar depression. Behav Res Ther 1993; 31:325–330 [B]
254. McLean P, Taylor S: Severity of unipolar depression and choice of treatment. Behav Res Ther 1992; 30:443–451 [A]
255. Rohde P, Lewinsohn PM, Seeley JR: Response of depressed adolescents to cognitive-behavioral treatment: do differences in initial severity clarify the comparison of treatments? J Consult Clin Psychol 1994; 62:851–854 [B]
256. Thase ME, Simons AD, Cahalane J, McGeary J, Harden T: Severity of depression and response to cognitive behavior therapy. Am J Psychiatry 1991; 148:784–789 [B]
257. Kendall PC, Morris RJ: Child therapy: issues and recommendations. J Consult Clin Psychol 1991; 59:777–784 [F]

258. Klerman GL, Weissman MM, Rounsaville BJ, Chevron ES: Interpersonal Psychotherapy of Depression. New York, Basic Books, 1984 [G]
259. Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, Glass DR, Pilkonis PA, Leber WR, Docherty JP, Fiester SJ, Parloff MB: National Institute of Mental Health Treatment of Depression Collaborative Research Program: general effectiveness of treatments. Arch Gen Psychiatry 1989; 46:971–982 [A]
260. Schulberg HC, Block MR, Madonia MJ, Scott CP, Rodriguez E, Imber SD, Perel J, Lave J, Houck PR, Coulehan JL: Treating major depression in primary care practice: eight-month clinical outcomes. Arch Gen Psychiatry 1996; 53:913–919 [A]
261. Markowitz JC, Klerman GL, Clougherty KF, Spielman LA, Jacobsberg LB, Fishman B, Frances AJ, Kocsis JH, Perry SW III: Individual psychotherapies for depressed HIV-positive patients. Am J Psychiatry 1995; 152:1504–1509 [B]
262. Markowitz JC, Kocsis J, Fishman B, Spielman LA, Jacobsberg LB, Frances AJ, Klerman GL, Perry SW: Treatment of depressive symptoms in human immunodeficiency virus-positive patients. Arch Gen Psychiatry 1998; 55:452–457 [B]
263. Hardy GE, Barkham M, Shapiro DA, Reynolds S, Rees A, Stiles WB: Credibility and outcome of cognitive-behavioural and psychodynamic-interpersonal psychotherapy. Br J Clin Psychol 1995; 34:555–569 [F]
264. Barber JP, Muenz LR: The role of avoidance and obsessiveness in matching patients to cognitive and interpersonal psychotherapy: empirical findings from the Treatment for Depression Collaborative Research Program. J Consult Clin Psychol 1996; 64:951–958 [B]
265. Bash M: Understanding Psychotherapy: The Science Behind the Art. New York, Basic Books, 1988 [G]
266. Bibring E: Psychoanalysis and the dynamic psychotherapies. J Am Psychoanal Assoc 1954; 2:745–770 [G]
267. Gray SH: Quality assurance and utilization review of individual medical psychotherapies, in Manual of Quality Assurance Review. Edited by Mattson MR. Washington, DC, American Psychiatric Press, 1992, pp 159–166 [F]
268. Blatt SJ: Contributions of psychoanalysis to the understanding and treatment of depression. J Am Psychoanal Assoc 1998; 46:722–752 [F]
269. Brenner C: Depression, anxiety and affect theory. J Psychoanal 1974; 55:25–32 [G]
270. Freud S: Mourning and melancholia (1917 [1915]), in Complete Psychological Works, standard ed, vol 14. London, Hogarth Press, 1957, pp 243–258 [G]
271. Kohut H: Thoughts on narcissism and narcissistic rage. Psychoanal Study Child 1972; 27:360–400 [G]
272. Zetzel ER: On the incapacity to bear depression (1965), in The Capacity for Emotional Growth. New York, International Universities Press, 1970, pp 82–224 [G]
273. Loewald HW: Perspectives on memory (1972), in Papers on Psychoanalysis. New Haven, Conn, Yale University Press, 1980, pp 148–173 [G]
274. Tasman A, Kay J, Lieberman JA: Psychiatry. Philadelphia, WB Saunders, 1996 [G]
275. Brenner C: Psychoanalytic Technique and Psychic Conflict. New York, International Universities Press, 1976 [F]
276. Rado S: The problem of melancholia (1927), in Psychoanalysis of Behavior: Collected Papers. New York, Grune & Stratton, 1956 [G]
277. Karasu TB: Developmentalist metatheory of depression and psychotherapy. Am J Psychother 1992; 46:37–49 [F]
278. Covi L, Lipman RS, Derogatis LR, Smith JE III, Pattison JH: Drugs and group psychotherapy in neurotic depression. Am J Psychiatry 1974; 131:191–198 [A]
279. Daneman EA: Imipramine in office management of depressive reactions (a double-blind study). Dis Nerv Syst 1961; 22:213–217 [A]
280. Beach SRH, Sandeen EE, O'Leary KD: Depression in Marriage. New York, Guilford, 1990 [G]

281. Yager J: Mood disorders and marital and family problems, in American Psychiatric Press Review of Psychiatry, vol 11. Edited by Tasman A, Riba MB. Washington, DC, American Psychiatric Press, 1992, pp 477–493 [G]
282. Coyne JC, Kessler RC, Tal M, Turnball J, Wortman CB, Greden JF: Living with a depressed person. J Consult Clin Psychol 1987; 55:347–352 [F]
283. Hahlweg K, Markman HJ: Effectiveness of behavioral marital therapy: empirical status of behavioral techniques in preventing and alleviating marital distress. J Consult Clin Psychol 1988; 56:440–447 [F]
284. Jacobson NS, Martin B: Behavioral marriage therapy: current status. Psychol Bull 1976; 83:540–556 [F]
285. Jacobson N, Addis M: Research on couples and couple therapy: what do we know? where are we going? J Consult Clin Psychol 1993; 61:85–93 [F]
286. O'Leary KD, Beach SR: Marital therapy: a viable treatment for depression and marital discord. Am J Psychiatry 1990; 147:183–186 [A]
287. Bright JI, Baker KD, Neimeyer RA: Professional and paraprofessional group treatments for depression: a comparison of cognitive-behavioral and mutual support interventions. J Consult Clin Psychol 1999; 67:491–501 [A]
288. Neimeyer RA, Baker KD, Haykal RF, Akiskal HS: Patterns of symptomatic change in depressed patients in a private inpatient mood disorders program. Bull Menninger Clin 1995; 59:460–471 [C]
289. Neimeyer RA, Feixas G: The role of homework and skill acquisition in the outcome of group cognitive therapy for depression. Behavior Therapy 1990; 21:281–292 [B]
290. MacKenzie RR: Anti-depression interpersonal psychotherapy groups (IPT-G): preliminary effectiveness data. Society for Psychotherapy Research Conference, 1999 [B]
291. Yalom ID: The Theory and Practice of Group Psychotherapy, 4th ed. New York, Basic Books, 1995 [G]
292. Smith ML, Glass GV, Miller TI: The Benefits of Psychotherapy. Baltimore, Johns Hopkins University Press, 1980 [G]
293. Toseland RW, Siporin M: When to recommend group treatment: a review of the clinical and group literature. Int J Group Psychother 1986; 36:171–201 [F]
294. Piper WE, Joyce AS: A consideration of factors influencing utilization of time-limited short-term group therapy. Int J Group Psychother 1996; 46:311–328 [F]
295. McRoberts C, Burlingame GM, Hoag MJ: Comparative efficacy of individual and group psychotherapy: a meta-analytic perspective. Group Dynamics: Theory, Research, and Practice 1998; 2:101–117 [E]
296. Targ EF, Karasic DH, Diefenbach PN, Anderson DA, Bystritsky A, Fawzy FI: Structured group therapy and fluoxetine to treat depression in HIV-positive persons. Psychosomatics 1994; 35:132–137 [B]
297. Lieberman MA, Borman LD: Self-Help Groups for Coping With Crisis. San Francisco, Jossey-Bass, 1979 [G]
298. Shapiro DA, Barkham M, Rees A, Hardy GE, Reynolds S, Startup M: Effects of treatment duration and severity of depression on the effectiveness of cognitive-behavioral and psychodynamic-interpersonal psychotherapy. J Consult Clin Psychol 1994; 62:522–534 [B]
299. Wexler BE, Cicchetti DV: The outpatient treatment of depression: implications of outcome research for clinical practice. J Nerv Ment Dis 1992; 180:277–286 [F]
300. Beck AT, Jallon SD, Young JE: Treatment of depression with cognitive therapy and amitriptyline. Arch Gen Psychiatry 1985; 42:142–148 [D]
301. Blackburn IM, Bishop S, Glen AI, Whalley LJ, Christie JE: The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. Br J Psychiatry 1981; 139:181–189 [A]

302. Chaudhry HR, Najam N, Naqvi A: The value of amineptine in depressed patients treated with cognitive behavioural psychotherapy. Hum Psychopharmacol 1998; 13:419–424 [A]
303. Hersen M, Bellack AS, Himmelhoch JM, Thase ME: Effects of social skill training, amitriptyline, and psychotherapy in unipolar depressed women. Behavior Therapy 1984; 15:21–40 [B]
304. Murphy GE, Simons AD, Wetzel RD, Lustman PJ: Cognitive therapy and pharmacotherapy: singly and together in the treatment of depression. Arch Gen Psychiatry 1984; 41:33–41 [A]
305. Thase ME, Greenhouse JB, Frank E, Reynolds CF, Pilkonis PA, Hurley K, Grochocinski VJ, Kupfer DJ: Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry 1997; 54:1009–1015 [E]
306. Fava GA, Grandi S, Zielezny M, Canestrari R, Morphy MA: Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry 1994; 151:1295–1299 [B]
307. Fava M, Kaji J: Continuation and maintenance treatments of major depressive disorder. Psychiatr Annals 1994; 24:281–290 [F]
308. Fava M, Davidson KG: Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996; 19:179–200 [F]
309. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P: Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry 1998; 55:816–820 [G]
310. Consensus Development Panel: NIMH/NIH Consensus Development Conference Statement: mood disorders: pharmacologic prevention of recurrences. Am J Psychiatry 1985; 142:469–476 [F]
311. Maj M, Veltro F, Pirozzi R, Lobrace S, Magliano L: Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 1992; 149:795–800 [B]
312. Thase ME, Simons AD, McGeary J, Cahalane JF, Hughes C, Harden T, Friedman E: Relapse after cognitive behavior therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry 1992; 149:1046–1052 [C]
313. Keller MD, Gelenberg AJ, Hirschfeld RM, Rush AJ, Thase ME, Kocsis JH, Markowitz JC, Fawcett JA, Koran LM, Klein DN, Russell JM, Kornstein SG, McCullough JP, Davis SM, Harrison WM: The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998; 59:598–607 [A]
314. Prien RF, Kupfer DJ: Continuation drug therapy for major depressive episodes: how long should it be maintained? Am J Psychiatry 1986; 143:18–23 [B]
315. Jarrett DB, Basco MR, Riser R, Ramanan J, Marwill M, Rush AJ: Is there a role for continuation phase cognitive therapy for depressed outpatients? J Consult Clin Psychol 1998; 66:1036–1040 [B]
316. Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R: Four-year outcome for cognitive behavioral treatment of residual symptoms in major depression. Am J Psychiatry 1996; 153:945–947 [B]
317. Solomon DA, Bauer MS: Continuation and maintenance pharmacotherapy for unipolar and bipolar mood disorders. Psychiatr Clin North Am 1993; 16:515–540 [F]
318. Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990; 47:1093–1099 [A]
319. Kupfer DJ, Frank E, Perel JM, Cornes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992; 49:769–773 [A]

320. Frank E, Kupfer DJ, Perel JM, Cornes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Comparison of full-dose versus half-dose pharmacotherapy in the maintenance treatment of recurrent depression. J Affect Disord 1993; 27:139–145 [A]
321. Scott J: Chronic depression: can cognitive therapy succeed when other treatments fail? Behavioural Psychotherapy 1992; 20:25–36 [B]
322. Belsher G, Costello CB: Relapse after recovery from unipolar depression: a critical review. Psychol Bull 1988; 104:84–96 [F]
323. Petrides G, Dhossche D, Fink M, Francis A: Continuation ECT: relapse prevention in affective disorders. Convuls Ther 1994; 10:189–194 [B]
324. Vanelle JM, Loo H, Galinowski A, de Carvalho W, Bourdel MC, Brochier P, Bouvet O, Brochier T, Olie JP: Maintenance ECT in intractable manic-depressive disorders. Convuls Ther 1994; 10:195–205 [C]
325. Dilsaver SC, Kronfol Z, Sackellares JC, Greden JF: Antidepressant withdrawal syndromes: evidence supporting the cholinergic overdrive hypothesis. J Clin Psychopharmacol 1983; 3:157–164 [F]