# CHAPTER 14. MOOD DISORDERS

# 14.7 MOOD DISORDERS: TREATMENT OF DEPRESSION

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Many available options now exist for treatment of mood disorders. Depressive disorders have enjoyed major therapeutic advances during the past decade, and the plethora of new options confronts clinicians with the problem of tailoring them to individual patients. Which strategies (types of treatment), applied in what order (strategic planning), and delivered by which methods (tactics) (e.g., dosage, duration) produce the best results for most patients in the shortest period of time? Specifying the objectives of each phase of treatment and careful, timely reappraisal of whether they are met, optimize patient outcomes.

Specific objectives of each treatment phase (i.e., acute, continuation, maintenance) provide a strategic map for managing these patients. For mood disorders, initial treatment objectives include (1) symptom remission (acute phase) and restoration of psychosocial functioning (acute and continuation phases), (2) prevention of a relapse (continuation phase), and (3) prevention of recurrences, or new episodes in patients with recurrent depressions (maintenance phase).

## STRATEGIES

When initiating acute-phase treatment, practitioners decide where the patient should be treated (e.g., outpatient, day hospital, or inpatient). Treatment location is dictated by factors such as (1) the imminent risk of suicide, (2) the capacity of the patient to recognize and follow instructions or recommendations (adherence, psychosis), (3) the level of psychosocial resources, (4) the level of psychosocial stressors, and (5) the level of functional impairment.

Next, one chooses among the four common acute-phase treatments (medication, psychotherapy, the combination of medication and psychotherapy, or electroconvulsive therapy [ECT]). For some, light therapy alone or in combination with medications may also be an option.

In general, patients who respond to acute-phase medication (alone or combined with psychotherapy) receive continuation-phase medication at the same dosage. Continuation-phase ECT may be indicated for acute-phase ECT responders if continuation-phase medication does not prevent relapse or if prior

medications have been ineffective, although the efficacy of this approach rests on open case series rather than randomized controlled trials of continuation-phase ECT.

While no randomized controlled trials of continuation-phase psychotherapy alone are available, a few open studies suggest that patients responding to acute-phase psychotherapy alone may further benefit from continuation-phase psychotherapy at less frequent intervals for the subsequent 6 to 8 months. The comparative efficacy of the combination of medication and formal psychotherapy during the continuation phase versus continuing medication only has not been investigated.

## TACTICS

Tactics are devised to ensure an adequate treatment trial (e.g., adequate dosage and duration of treatment). Adequate implementation is required to determine whether any strategic choice was correct. Adherence is the most important tactical issue. Low adherence may be due to adverse effects, the conscious or unconscious meaning of taking medication, or the desire to leave treatment once improved (perhaps because of the shame and stigma that still surround psychiatric disorders).

A second key tactical issue is adequate evaluation of whether the objective (i.e., symptom remission) was met. Symptom severity may be gauged by careful interviewing or by use of a rating scale. For mood disorders, a serious difficulty is accepting a partial response in place of a full remission, a risk for any acute-phase treatment. A full remission carries a better prognosis and minimal residual symptoms.

## STRATEGIC CHOICES

**Medication** The available antidepressants differ in their pharmacology, drug-drug interactions, and short- and long-term adverse effects. They do not differ in overall efficacy, speed of response, or long-term effectiveness. Substantial evidence shows that failure to tolerate or respond to one medication does not imply failure with other medications. In fact, a shift from one medication class to another carries 1 in 2 chance of response to both the initial medication and to the next medication if the first fails to provide a satisfactory response.

**Psychotherapy** Formal psychotherapy aims at particular objectives. General clinical management, part of any treatment, includes explaining the diagnosis, treatment plan, treatment objectives, anticipated treatment period, counseling, management of both adherence and adverse effects, and a regular assessment of whether or not the treatment objectives are being met. It may involve consulting both the patient and significant others.

The objectives of formal psychotherapy used alone to treat mood disorders are identical to those for medication: (1) symptom remission; (2) psychosocial restoration; and (3) prevention of relapse or recurrence. When used in combination with medication, psychotherapies can achieve such additional objectives as reducing the secondary psychosocial consequences of the disorder (e.g., marital discord, occupational difficulties) or increasing medication adherence.

Clinical management aims to increase adherence, but formal psychotherapy can also be beneficial. Individuals who may need more-formal adherence counseling include those with significant prior or current adherence difficulties and those with relatively fixed negative attitudes toward a clearly indicated treatment. Formal psychotherapy to address the psychosocial consequences of the disorder may include individual, family, couples, or occupational approaches. Evidence suggests that used in combination with medication to control symptoms, such treatments improve the targeted difficulty (e.g., marital counseling improves marriages).

Psychotherapy as monotherapy for symptom remission has shown greater efficacy than wait-listing controls in studies of less severely or chronically ill, nonpsychotic, depressed outpatients. In addition, while some evidence suggests that psychotherapy alone as a maintenance treatment has some benefit in prolonging the well interval, in general, when maintenance treatment is anticipated, medications (alone or combined with psychotherapy) are preferred, given the larger number of medication maintenance studies supporting efficacy.

**Choosing Among Psychotherapies** No established clinical predictors exist to guide selection of a psychotherapy. Cognitive therapy may be slightly less effective in those with more-dysfunctional attitudes, while interpersonal psychotherapy may be somewhat less effective in those with more-interpersonal problems. However, these predictors lack clinical utility. Time-limited therapies are usually preferred over time-unlimited therapies for symptom reduction because they have established efficacy (time-unlimited therapies do not) and because medication is an effective alternative if psychotherapy alone fails.

Some believe that reconstructive (time-unlimited) psychotherapies are more useful in the treatment of Axis II disorders, while reeducative therapies may be more useful with Axis I conditions. No evidence favors use of psychotherapy alone over medication when a concurrent Axis II disorder exists. On the other hand, psychotherapeutic tactics may benefit the medication management of depressed patients with Axis II conditions by ensuring adherence. Logically, psychotherapy, if used alone, should be tried for a finite time period and outcome should be evaluated, just as with medication.

Declaration of psychotherapy failures is largely based on lack of efficacy, although a few patients discontinue treatment unilaterally. When to declare psychotherapy a failure is a complex problem. Some patients respond early, while others may take 8 to 10 weeks. The premature discontinuation rate may be higher in actual practice than it is in efficacy trials. Just as with medication, if a symptomatic patient inappropriately discontinues treatment, one should actively attempt to reengage them since the depression has not remitted and, consequently, the prognosis is poor.

What treatment should follow if psychotherapy alone is ineffective? Medication, given its established efficacy, is the next best logical step. The psychotherapy may be continued or discontinued when medication is begun. Whether a different form of psychotherapy would be effective if the initial psychotherapeutic approach has not been tested.

## COMBINED TREATMENT

Medication and formal psychotherapy are often combined in practice, yet data from randomized controlled trials suggest that the combination does not predictably add to the symptom-reducing effects of either treatment alone, at least in less complex, chronically ill patients. Conversely, the combination may result in both symptom reduction and psychosocial restoration, which is an additional rationale for using the combined approach. There are basically three ways to develop a combined treatment: (1) initiate the combination as acute-phase treatment, (2) add formal psychotherapy to medication that has elicited a partial response (particularly when there are residual cognitive, psychological, or interpersonal symptoms or difficulties), or (3) add medication after a partial response to psychotherapy alone.

Using the combination of medication and formal psychotherapy at the outset of acute-phase treatment is called for if either (1) formal psychotherapy is used to increase adherence, while medications are used for symptom control or (2) if the targets of each treatment were somewhat distinct and both needed early remediation (e.g., medication for the depressive symptoms and psychotherapy for marital problems). In addition, clinical experience suggests that combination treatment may be preferable to either treatment

alone with (1) a coexisting Axis II disorder, (2) a chronic and recurrent pattern with poor interepisode recovery, or (3) a patient who is discouraged and demoralized as well as clinically depressed.

Diagnosis and medication management must allow time for patients with little prior treatment to collaborate in the optimal use of medication. Thus, it is often simpler to initiate medication and clinical management and then determine whether formal psychotherapy is indicated either for complete symptomatic remission or to address psychosocial problems unrelieved by medication. For example, psychotherapy might be added after a partial medication response (e.g., persistence of cognitive and interpersonal difficulties).

When to add psychotherapy to medication is unclear. Evidence suggests that psychosocial and occupational improvements follow response. Thus, routine use of both treatments initially may not be necessary for psychosocial restoration. The need for adjunctive psychotherapy to redress psychosocial difficulties becomes clearer the longer symptom remission obtains and psychosocial problems persist. A history of long-standing psychosocial difficulties, even during remission of chronic depression, may suggest either beginning with combined treatment or adding psychotherapy shortly after symptoms are controlled with medication.

When combined treatment does not produce a full response, a switch of medication classes with continued psychotherapy is logically the next step, since evidence indicates that switching medication classes is effective.

## ELECTROCONVULSIVE THERAPY

ECT is effective, even in patients who have failed to respond to one or more medications or combined treatment. It is effective in both psychotic and nonpsychotic forms of depression. Usually, 8 to 12 treatments are needed. Bilateral ECT is somewhat more effective than unilateral ECT, but it appears to have more cognitive adverse effects.

## OTHER TREATMENTS

Light therapy has been most clearly evaluated in mood disorder with seasonal pattern, either as monotherapy or in combination with medication. Patients who respond do so within 2 to 4 weeks.

## STRATEGIC ISSUES

**Role of Diagnosis in Treatment Selection** Maintenance medication effectively prevents recurrences of dysthymic disorder, complicated by recurrent major depressive episodes or not. Psychotic depression usually requires both an antidepressant and an antipsychotic agent. Alternatively, ECT is useful in psychotic depression, either as a first-line treatment or after medication has proven ineffective. For those with atypical features, strong evidence indicates that tricyclic drugs are less effective than the monoamine oxidase inhibitors (MAOIs). There is some suggestion of efficacy for the selective serotonin reuptake inhibitors (SSRIs) in atypical depression.

The concurrent presence of another disorder may also affect initial treatment selection. Presence of nonmood Axis I disorder favors use of medications with demonstrated efficacy in both the mood and nonmood disorder. For example, effective treatment of obsessive-compulsive disorder with depressive symptoms usually results in remission of the depression. Similar findings have been reported for anorexia nervosa and bulimia. When panic disorder co-occurs with major depressive disorder, medications with demonstrated efficacy in each condition are preferred (e.g., tricyclic drugs, SSRIs). In

general, the nonmood disorder dictates the choice of treatment.

Concurrent substance abuse raises the possibility of a substance-induced mood disorder, which must be evaluated by history or after several weeks of abstinence, since abstinence results in remission of depressive symptoms in substance-induced mood disorders. If significant depressive symptoms continue, even with abstinence, an independent mood disorder is diagnosed and treated.

Axis II disorders frequently accompany mood disorders, but diagnosis of Axis II disorders remains tentative in the presence of a clinical depression. An Axis II disorder should not be mistaken for recurrent major depressive disorder with poor interepisode recovery, since the treatment objectives and strategies differ.

An Axis II disorder does not contraindicate treating the mood disorder, but its presence may prolong the time to acute-phase treatment response, interfere with adherence, or even preclude full symptomatic remission. In general, the presence of Axis II disorders suggests a less optimistic prognosis, because circumstantial evidence suggests that Axis II disorders are risk factors for subsequent relapse or recurrence.

Axis II disorders raise other tactical issues, such as adherence, establishing a therapeutic alliance, or long-term management. In addition, the response to either medication or time-limited psychotherapy is slower, less complete, or both in the presence of an Axis II disorder.

General medical conditions commonly accompany mood disorders and are established risk factors in their development. Recent evidence indicates that a major depressive episode is associated with increased morbidity or mortality of some associated general medical conditions.

Principles that apply to the treatment of depression without a general medical condition generally apply when these conditions are present. However, treatment strategies and tactics are more complex. The initial choice of treatment is influenced by prior response to antidepressant treatments, the relative medical safety of medications, and clinical judgment about whether psychotherapeutic methods might particularly benefit some of these patients. The tactical choice of medications is affected by drug interactions, the pharmacological profile of the compound, the general medical condition, and drug dosing requirements.

Complex, ongoing, stressful life events or social contextual issues (often profoundly disturbing to patients) should not influence whether or not medication is used. Often, patients in major depressive episodes whose symptoms are reduced by medication become less disabled from the mood disorder and are better able to manage these complex life circumstances. On the other hand, chronic, disturbing, life circumstances (e.g., chronic marital discord, spousal abuse) argue for stronger consideration of combined treatment, either initially or sequenced, to obtain both symptom remission and psychosocial restoration. Table 14.7-1 summarizes the relation between clinical diagnoses and treatment selection.

**Table 14.7-1** Relation of Diagnosis to Treatment Selection

| Diagnosis | Treatment Recommendations |
|---|---|
| Major depressive disorder (mild-to-moderate severity) | Medication or time-limited, depression-targeted psychotherapies[a]<br>No maintenance-phase treatment |
| Major depressive disorder, recurrent | Consider maintenance-phase treatment |
| Major depressive disorder with psychotic features | Antipsychotic plus antidepressant medication<br>Electroconvulsive therapy |
| Major depressive disorder with melancholic or severe features | Medications essential<br>Nortriptyline drugs preferred<br>Monoamine oxidase inhibitors have established efficacy |
| Depression with atypical features | |
| Depression with seasonal pattern | Light therapy or medications |
| Dysthymic disorder | Medications; time-limited, depression-targeted psychotherapies; or their combination<br>Consider maintenance-phase therapy |
| Complex[b] or chronic depressions | Medication plus psychotherapy[a] |

[a] Interpersonal psychotherapy, cognitive therapy, or behavior therapy.
[b] Complex refers to depression co-occurring with other psychiatric conditions (e.g., anxiety disorders, Axis II conditions).
[c] Psychotherapy may aim at adherence enhancement, symptom reduction, relapse prevention, or psychosocial restoration.

**Selecting Initial Treatment** In general, about 45 to 60 percent of all outpatients with nonpsychotic major depressive disorder who begin treatment with medication, psychotherapy, or the combination respond. Consequently, roughly one-half of patients should anticipate a second treatment trial if the initial treatment selected is either intolerable or ineffective. Selection of the initial treatment depends on the chronicity of the condition, the history of recurrences (which predicts the likelihood of future recurrences), family history of illness, symptom severity, associated comorbid general medical or other psychiatric conditions, prior treatment responses to other acute-phase treatments, and patient preference. In general, the less severe, less chronic, and less complex the depression (i.e., less current comorbidity), the greater the role for patient preference, since evidence for selecting between time-limited, depression-targeted psychotherapy and medication is lacking. Furthermore, it is believed that the combination of medication and formal psychotherapy is less likely to be needed for milder, uncomplicated depressions.

Moderate-to-severe mood disorders with prominent chronicity or prior recurrences generally require maintenance treatment. Since medications are the maintenance treatments with established efficacy, medication treatment (alone or combined with psychotherapy) is recommended.

The evidence for the efficacy of medication alone in more-severe depressions is clear; psychotherapy alone is less well studied. Psychotherapy alone appears to be less predictably effective than medication in outpatients with endogenous or melancholic symptom features. Whether psychotherapy alone is effective in depressions with atypical symptom features is under study. However, the MAOIs and SSRIs have established efficacy in this group.

**Selecting Second Treatment Options** If the first treatment fails (e.g., due to intolerance or lack of efficacy), a strategic decision on the second treatment after the differential diagnosis (including occult general medical condition or substance abuse) has to be reconsidered.

For those receiving medication initially, dose adjustments, extending the trial period, switching to an alternative treatment (either medication or psychotherapy), or adding a second treatment to the initial one are common options. Factors recommending dose escalations are (1) no adverse effects, (2) a prior history consistent with rapid drug metabolism, or (3) low therapeutic blood concentrations. However, blood concentrations of newer-generation medications are related to outcome although they are for desipramine (Norpramin, Pertofrane), imipramine (Tofranil), and nortriptyline (Pamelor). Extending the initial trial is indicated if (1) it has been less than 6 weeks, (2) there is a partial response by 6 weeks, or (3) prior medication trials were unsuccessful and shorter than 6 weeks.

Likewise, partial response to psychotherapy by week 6 argues for extending the trial period. Nonresponse by 8 weeks often predicts an ultimate poor response. Extending a trial of light therapy beyond 3 weeks in nonresponders has not been evaluated. Clinical experience suggests that extending ECT beyond 10 trials with complete nonresponse is unlikely in most cases to elicit a subsequent response, although careful studies are lacking.

The choice to switch from the initial single treatment to a new single treatment (as opposed to adding a second treatment) depends on the philosophy guiding the clinician, the patient's prior treatment history, and other clinical issues. The best-documented augmentation strategies involve inexpensive medicines (e.g., lithium or thyroid hormones) and response, if it occurs, is often within 2 weeks. Conversely, a switching strategy sometimes involves a washout period (e.g., switching from fluoxetine [Prozac] to an MAOI) for safety reasons as well as the need to wait longer than 2 weeks for a full effect. Alternatively, how long to continue augmentation is not clear, and lithium augmentation entails some expense and inconvenience (i.e., blood concentration monitoring).

If the initial trial is the patient's first treatment and other clinical or economic reasons favor monotherapy, switching rather than augmenting is preferred. On the other hand, augmentation strategies, particularly the use of two different medications, seem effective in patients who have failed one or more well-conducted single medication trials. Thus, switching might be preferable for those with only one or two prior treatment attempts, while augmentation is preferable for those who have failed several single-treatment trials. Recent reviews indicate that if the initial medication is ineffective or cannot be tolerated, it is reasonable to switch medication classes. In psychiatric settings, augmentation may be preferable, since more psychiatric patients have failed several adequate prior single treatments.

The value of augmenting medication with psychotherapy is not well evaluated. Many clinicians believe that if the residual symptoms after a partial response to medication are largely cognitive or psychological, either augmentation with psychotherapy or prolonging the initial medication trial are preferred to switching medications or augmenting with another medication, based on the assumption that these symptoms represent residual psychosocial sequelae. On the other hand, if anhedonia persists after an initial medication trial, switching or augmentation with another medication rather than psychotherapy is often preferred since such symptoms suggest ongoing limbic/paralimbic system dysfunction. However, these suggestions are largely based on clinical experience rather than scientific evidence.

## TACTICAL ISSUES

The strategic choices of treatment focus on selection of the initial therapy, or for those who fail the initial therapy, the selection of a second treatment option. Implementation of these strategies requires (1) careful attention to adherence, (2) careful evaluation of outcome, (3) proper dosing and duration of the trial, and (4) timely declaration of treatment failure.

**Adherence** Treatment adherence is increased if patients understand anticipated objectives and common strategies, if fewer daily doses are required (e.g., once-a-day versus three-times-a-day dosing), and no personality disorder is present. Evidence also suggests more-frequent early visits (e.g., weekly versus monthly) improve adherence. Whether other current psychiatric conditions affect adherence is unclear; it is not related to gender, educational level, or socioeconomic status. The best predictor of future adherence is prior adherence.

Thus, general clinical management of medication treatment should include discussions with patients (and, potentially, significant others) about the objectives of treatment, anticipated treatment period, and adherence obstacles. It is best to anticipate and identify obstacles to adherence prior to prescribing medication or initiating psychotherapy and to make adherence checks a routine part of each visit.

Initially, visits should be frequent enough to ensure adherence and permit timely intervention for adverse effects. Several brief telephone contacts during the initial weeks of treatment help adherence by reassuring patients, ensuring that adverse effects are avoided, countering demoralization and pessimism

that impairs adherence, and providing information to overcome short-term concentration and recall problems that are part of depressive episodes.

**Choosing Among Medications** If medication (alone or in combination with psychotherapy) is part of the first step, the practitioner must select from a variety of available compounds. Medications differ in their short- and long-term adverse effects and spectrum of action but not in overall efficacy or speed of response. If maintenance medication is anticipated, long-term adverse effects are more important than short-term effects in selection (e.g., tertiary tricyclic drugs are associated with greater weight gain than SSRIs over the long run).

Table 14.7-2 lists commonly used antidepressant agents presently available in the United States and groups them on the basis of their presumed mechanisms of action (e.g., presynaptic or postsynaptic activity). However, as basic neuroscientific knowledge expands, further actions will likely be discovered. For example, the number of serotonin receptor types has increased faster than our understanding of their physiological roles. Further, the actions of some (e.g., venlafaxine [Effexor]) are affected by the dosages used or levels attained in the central nervous system (CNS). Venlafaxine exerts proportionally more serotonin than norepinephrine reuptake blockade at lower dosages than at higher dosages.

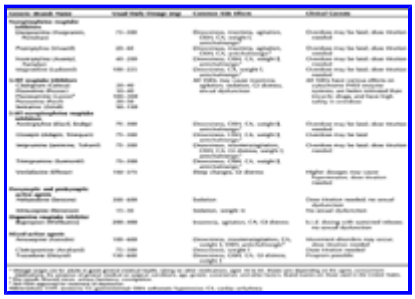
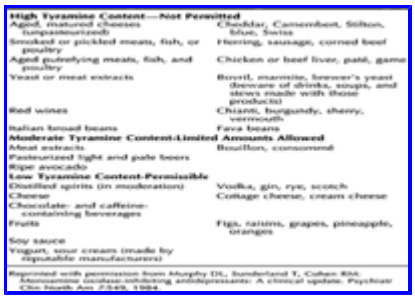


**Table 14.7-2** Antidepressant Medications*

Table 14.8-2 lacks two commonly used drug combination treatments (lithium plus antidepressants and liothyronine [Cytomel] augmentation of tricyclic drugs). A Table 14.8-2 provides selected clinical caveats. This list is not exhaustive. Drug-drug interactions, at either the neuronal level (pharmacodynamics) or at the level of absorption, metabolism, and excretion (pharmacokinetics) affect selection of agents, their dosing, and ultimately the risk-benefit equation for individual patients. Patients should be advised what adverse effects to anticipate and encouraged to report them as early as possible. Management of adverse effects may include lowering the dosage, switching medications, or treating the adverse effects with an additional medication.

The MAOIs (tranylcypromine [Parnate] and phenelzine [Nardil]) still have a role in the treatment of depression, the depressed phase of bipolar disorders, and in depressions unresponsive to other treatments. However, because of the necessity of regulating diet (Table 14.7-3) and evaluating concomitant medications (Table 14.7-4), the MAOIs are not used as first-line drugs.

**Table 14.7-3** MAOI Dietary Restrictions



| | |
|---|---|
| **High Tyramine Content—Not Permitted** | |
| Aged, matured cheeses (unpasteurized) | Cheddar, Camembert, Stilton, blue, Swiss |
| Smoked or pickled meats, fish, or poultry | Herring, sausage, corned beef |
| Aged putrefying meats, fish, and poultry | Chicken or beef liver, paté, game |
| Yeast or meat extracts | Boril, marmite, brewer's yeast (beware of drinks, soups, and stews made with these products) |
| Red wines | Chianti, burgundy, sherry, vermouth |
| Italian broad beans | Fava beans |
| **Moderate Tyramine Content-Limited Amounts Allowed** | |
| Meat extracts | Bouillon, consommé |
| Pasteurized light and pale beers | |
| Ripe avocado | |
| **Low Tyramine Content-Permissible** | |
| Distilled spirits (in moderation) | Vodka, gin, rye, scotch |
| Cheese | Cottage cheese, cream cheese |
| Chocolate- and caffeine-containing beverages | |
| Fruits | Figs, raisins, grapes, pineapple, oranges |
| Soy sauce | |
| Yogurt, sour cream (made by reputable manufacturers) | |

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| | |
|---|---|
| **Generally Contraindicated Hazardous Potentiations*** | |
| Stimulants | Weight-reducing or antiappetite drugs; amphetamine, cocaine |
| Decongestants | Sinus, hay fever, and cold tablets; nasal sprays or drops; asthma tablets or inhalants; cough preparations (or any products containing ephedrine, phenylpropanolamine |
| Antihypertensives | Methyldopa, guanethidine, reserpine |
| Tricyclics | Imipramine, desipramine, chlorpromine |
| MAOIs | Tranylcypromine, after other MAOIs |
| Sympathomimetics | Dopamine, Metaraminol |
| Amine precursors | L-dopa, L-tryptophan |
| Narcotics | Meperidine (Demerol) |
| **Some Potentiation Possible** | |
| Opioids | Morphine, codeine |
| Sedatives | Alcohol, barbiturates, benzodiazepines |
| Local anesthetics containing vasoconstrictors | |
| Sympathomimetics | Ephedrine, norepinephrine, isoproterenol |
| General anesthetics | |

* Under certain circumstances, some of these drugs may be used together with MAOIs in specialized treatment approaches and with additional precautions. For example, tricyclics and L-tryptophan have been used with MAOIs in antidepressant regimens. Also of note, other agents from these drug classes are safely used (for example, the antihypertensive agent chlorothiazide) as only mild potentiation occurs.

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**Table 14.7-4** MAOI Drug Incompatibilities

Among the tricyclic medications, the secondary amines (desipramine or nortriptyline) have fewer adverse effects than the tertiary amines. Since nortriptyline has a well-established therapeutic window, drug concentration monitoring can ensure that patients who need minimal medication exposure obtain a therapeutic concentration. Conversely, the upper limit of the nortriptyline window may be a disadvantage when deciding to switch or augment treatments, as the blood concentrations may be used to declare a nonresponse.

Choosing more-sedating antidepressants (e.g., amitriptyline [Elavil, Endep]) for more-anxious depressed patients, or more-activating agents (e.g., desipramine) for those more psychomotor retarded is not based on evidence of differential efficacy. However, some clinicians believe that such choices based on adverse-effect profiles increase adherence in the initial weeks of treatment. That is, patients with marked insomnia and anxiety obtain some immediate relief from these associated symptoms before the full antidepressant effect of the drug appears and thus are more likely to comply with acute-phase treatment. These clinical observations are not supported by empirical data, however. In fact, attrition associated with paroxetine (Paxil) or fluoxetine (less-sedating drugs) is lower in acute-phase treatment than that with imipramine or amitriptyline (more-sedating drugs). In addition, the longer-term cost of a possibly beneficial short-term adverse effect advantage must be considered. For example, initially sedating antidepressants often continue to be sedating in the longer run, which may lead patients to prematurely discontinue continuation or maintenance phase treatment, thus increasing the risk of relapse or recurrence.

Some practitioners combine adjunctive medications (e.g., hypnotics or anxiolytics) with antidepressants to provide more immediate symptom relief either routinely from the outset or when the need for such adjunctive medications arises in an individual patient. Adjunctive medications used briefly to cover adverse effects to which most patients ultimately adapt can be useful. Conversely, discontinuing adjunctive medications can result in some return of symptoms or adverse effects to which the patient has not adapted.

Several disadvantages are associated with the routine use of adjunctive medications: (1) the potential risk, inconvenience and expense of unnecessary medications (i.e., many patients may not require them); (2) difficulty identifying the cause of medication intolerance or adverse effects (e.g., an allergic rash)

when treatment with an antidepressant and an adjunctive medication is begun at the same time; (3) difficulty in judging response to the antidepressant medication alone if adjunctive medication addresses critical symptoms used to gauge the success of acute-phase treatment, (discontinuing the adjunctive medication to see if the apparent response holds on the antidepressant alone may unnecessarily increase the number of visits or delay a timely revision in the treatment plan); and (4) adjunctive medications may cover adverse effects that if observed would lead to either a dose reduction or to switching treatments. For example, a sedative-hypnotic agent used in conjunction with an SSRI may inappropriately delay a strategic decision to either decrease the dosage or switch to an alternative agent.

In addition to adverse effects, medication choice is affected by prior history of response, cross-sectional symptom features, patient preference, dosing convenience (which affects adherence), drug interactions (if patients are, or will be, taking other medications), current general medical conditions (making one adverse-effect profile preferred over another), and a family history of response. A patient's prior treatment history is important because prior response typically predicts current response. In addition, a documented failure on a properly conducted trial of a particular antidepressant class (e.g., SSRIs, tricyclics, or MAOIs) suggests choosing an agent from an alternative class. Switching classes for those who fail on one class appears to be associated with roughly a 50 percent response rate with the second class of drugs.

History of a first-degree relative responding to a tricyclic drug or an MAOI is associated with a better response to the same class of agents in the patient. Whether family history of response predicts response to the newer antidepressant compounds is not known.

**Dosage and Duration** Tactical issues surrounding medication use include dosing steps, drug metabolism, pharmacokinetics, drug interactions, and adverse effects. The tricyclic drugs typically are initially given at low dosages and increased to the maximally tolerated dosage or (in the case of nortriptyline) until a therapeutic concentration is obtained. Gradual dose escalations are important to ensure adherence and avoid severe initial adverse effects. Thus, the tricyclic drugs require visits roughly once a week for outpatients as dosages are adjusted. Tricyclic blood concentration monitoring may reduce dosage adjustment time. Dosing is less complicated for the SSRIs than for the tricyclic drugs; fewer dose increments are needed, and the proper dosage is attained earlier because of their better adverse-effect profiles. Some newer agents (e.g., SSRIs, bupropion [Wellbutrin]) need fewer dosage adjustments, but with others (e.g., venlafaxine and nefazodone [Serzone]), raising the dosage increases the likelihood of response, so several adjustments are often helpful.

Safety in overdose is an issue, especially early in treatment. Thus, a 1-week prescription is recommended (without refills) so patients return for frequent medication visits when adverse effects and dosage levels are managed. Tricyclic drugs account for a greater percent of completed suicides than the newer agents, which are far safer in overdose.

**Evaluation of Outcome** The objective of acute-phase treatment (medication, psychotherapy, their combination, or ECT) is symptom remission, not just symptom reduction. Partial response is associated with a stormier prognosis. Thus, careful interviewing for criterion symptoms at each visit is essential. Self-reported or clinician-rated instruments can facilitate this assessment. Often the patient is slower to recognize the early therapeutic effect of the treatment than the clinician. Thus, a clinician-rated scale may be preferred to a self-reported instrument.

**Timely Declaration of Treatment Failures** Growing evidence indicates that acute phase medication trials should last 6 (and preferably 8) weeks to determine the full extent of symptom reduction attainable, although most (but not all) patients who ultimately respond fully show at least a partial response by weeks 3 or 4 if the dose is adequate during the initial weeks of treatment. Clinical

impression and recent reports suggest that no response by 3 to 4 weeks (e.g., <25 percent reduction in symptoms) indicates that a treatment change is needed (i.e., a few patients respond over the next several weeks), assuming an adequate dosage in the initial 3 to 4 weeks.

Each treatment step should be applied optimally (e.g., dosage and duration) to determine its effectiveness. There is a clinically important tension involved in evaluating the initial treatment—providing sufficient treatment for a long enough time to determine whether it is effective, while at the same time not prolonging (or overdosing) ultimately ineffective treatment.

Medication dosage obviously affects clinical outcome and adverse effect burden. Some patients metabolize certain drugs more rapidly or more slowly than others. Slow metabolizers, especially for the more anticholinergic tricyclic drugs, encounter adverse effects earlier in treatment or at lower dosages. High blood concentrations may cause arrythmias, seizures, or delirium. Fast metabolizers may exhibit virtually no adverse effects or benefits, even with rather large dosages. However, adverse effects, especially for desipramine and nortriptyline, do not predict blood concentrations. Indeed, orthostatic hypotension can occur even with low blood concentrations. Such cases argue for the value of a therapeutic blood concentration to determine dosing strategies, especially when tricyclic drugs are used in medically fragile patients.

Patients may not respond to a medication because (1) they cannot tolerate the adverse effects, even with a good clinical response; (2) an idiosyncratic adverse event occurs; or (3) the clinical response is not adequate. Idiosyncratic or serious adverse effects (e.g. seizures, allergic reactions), while rare, are most likely to be encountered in the first several weeks of treatment and often occur with dosage escalation or as medication concentrations rise to a steady-state level. Some of these adverse effects are dose dependent (e.g., sedation) and can be reduced by decreasing the dosage or slowing the rate of escalation. Moderate adverse effects, when encountered, argue for holding the dosage constant and allowing time for physiological adaptation, which often reduces adverse effects. Some adverse effects are less dose dependent (e.g., orthostatic hypotension), and tolerance to them is less likely. In these cases, gradual dosage escalation is less useful, and a change in treatment is often indicated.

Lack of efficacy is the most common reason for medication failure, but this cannot be fully gauged until patients have had several weeks of treatment at adequate dosages (4 to 6 weeks). Thus, careful evaluation of symptoms during acute-phase treatment (whether formally conducted with a rating scale or informally by assessing each criterion symptom of the mood disorder) is a useful gauge of the adequacy of medication response.

## CONTINUATION TREATMENT

Continuation treatment typically lasts 4 to 9 months. In theory, the duration depends on an estimate of when the episode would have remitted spontaneously. Thus, patients with longer prior episodes (e.g., 9 to 15 months) who have had only 2 months of a current depression, for example, would be candidates for 5 to 11 months of continuation treatment, assuming that acute treatment lasted 2 months. Follow-up studies of those with psychotic depressions 1 year after acute-phase treatment indicate a poorer prognosis than for nonpsychotic depression. Thus, continuation-phase treatment for psychotic depressions should be longer.

Continuation-phase medication treatment should end with a gradual taper of medication and careful symptom assessment during, and for several months following, discontinuation. When medication is used alone or in combination with formal psychotherapy for acute-phase treatment, continuation medication treatment is recommended, because early medication discontinuation is associated with a

higher relapse rate than later discontinuation. Whenever clinically feasible, continuation medication should be at the dosage used during acute-phase treatment. This recommendation is based on evidence from maintenance trials using lower-dosage tricyclic drugs, which suggested a higher recurrence rate than was obtained with full-dosage treatment.

Psychotherapy may be added to continuation-phase medication if psychosocial residua do not remit with medication alone. Whether to continue psychotherapy following response to acute-phase combined treatment is unclear and is entirely a matter of clinical judgment at this time. Continuation-phase psychotherapy alone (after acute-phase response to psychotherapy alone), has only indirect evidence of efficacy.

## MAINTENANCE TREATMENT

**Strategic Issues** Maintenance treatment aims at preventing new episodes (recurrences). It is appropriate for recurrent (but not for single episode) major depressive disorder. Maintenance medication treatment has been found effective in virtually all studies to date. Strong evidence indicates that those with three or more episodes should receive maintenance-phase treatment, and indeed even at 5 years, maintenance medication has prophylactic efficacy.

Whether those with only two major depressive episodes should receive maintenance treatment is less clear. Information that helps with this decision includes poor recovery between the two episodes, presence of two episodes within the last 3 years, or a positive family history for depression or bipolar disorder; any of these factors increase the likelihood of recurrence. However, clinicians and patients must decide collaboratively whether to initiate maintenance treatment or provide more-diligent monitoring with no treatment until a need is established by the development of a new episode. If a new episode develops when the patient is free of treatment, early intervention shortens the length of the new episode.

**Tactical Issues** An important issue in both continuation and maintenance treatment is symptom breakthrough, which may be modest and time-limited, requiring only minor shifts in the treatment plan (e.g., dosage adjustment, reassurance). On the other hand, if symptom breakthrough is profound or prolonged or does not respond to dosage adjustment and reassurance, it must be treated. No randomized controlled trials have addressed this issue. Perhaps the simplest approach is to augment the current medication with an additional one (e.g., lithium, thyroid hormone, or another antidepressant). If this strategy is effective, then the augmenting medication may be discontinued after a time, to determine whether it is necessary over the longer term. If the augmenting medication fails, then a switch in treatment to another medication may be needed.

Symptom breakthrough could also be remediated by psychotherapy, but this option has not been formally studied. Perhaps psychotherapy is indicated if the symptoms were caused by disturbed interpersonal relationships or life events (e.g., divorce or unemployment).

Another tactical problem encountered in both continuation and maintenance treatment is the management of the depression when intercurrent general medical illnesses requiring medication, surgery, or pregnancy occur. For patients who need a “window in time” for surgery or pregnancy, medication discontinuation should be gradual. Pregnancy lasts for a prolonged period and given the evidence for the efficacy of interpersonal therapy alone as a maintenance treatment, psychotherapy without medication may provide an extended drug-free period. The development of other general medical illnesses and the need for nonpsychotropic medications during continuation or maintenance treatment is not uncommon. These circumstances need to be managed with consideration of the

pharmacokinetics and drug interactions between the psychotropic and nonpsychotropic agents.

When to discontinue maintenance medication treatment is unclear. As noted above, a recently completed study in patients with highly recurrent depressions (more than three episodes) indicates the efficacy of maintenance treatment continues for at least 5 years. Some patients may require very prolonged (e.g., a decade) or even lifetime maintenance medication treatment. Discontinuation requires careful monitoring, because the first 6 months following discontinuation appear to be a particular risk period for recurrences.

## PATIENT PREFERENCE

Patients should become more informed about depressive disorders and their treatment. Even so, some patients are adamantly opposed to medication, while others are equally opposed to psychotherapy. Patient preference can play a greater role when evidence does not strongly support a specific choice. While patients may exercise their first preference initially, a contingency plan should be developed early in the management of the patient in case a second treatment trial is needed. Therefore, it might be wise to plan at the outset for at least two short-term treatment trials, to avoid inappropriate discouragement and consequent premature attrition if the initial treatment fails to provide full remission. Treatment tactics to optimize outcome include attention to adherence, careful titration of medication to attain maximal benefit with minimal adverse effects, and careful symptom evaluation to ensure that remission, not just improvement, has occurred. Establishing explicit goals and following a stepwise plan to attain them can help both practitioners and patients obtain the best outcomes.

## SUGGESTED CROSS-REFERENCES

Classification of mental disorders is discussed in Chapter 9, treatment of mood disorders in Chapter 14, psychotherapies in Chapter 30, biological therapies in Chapter 31, mood disorders and suicide in children in Chapter 45, and diagnosis and treatment of psychiatric disorders in late life in Chapter 51.

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