8 General Principles for Treatment of Unipolar Depression

Essential Concepts

- Antidepressants should lead to treatment response in most cases of acute unipolar depression, but treatment remission occurs in only about half of patients.
- Long-term benefits of antidepressant usage are less well established than acute efficacy.
- The utility of antidepressants has not been well established, and in the absence of better research, they may be considered doubtful in long-term management of *neurotic depression*, that is, a mixture of generalized anxiety and chronic dysthymia without a classic course of recurrent major depressive episodes.
- Cognitive behavioral psychotherapy and interpersonal psychotherapy are the two main kinds of psychotherapies studied empirically to treat depression.
- These psychotherapies appear equally effective to antidepressants in the first or second episode of a unipolar depressive illness; in later episodes, antidepressants are usually needed, although psychotherapies provide adjunctive benefit.
- Psychotherapies, frequently without antidepressants, are likely also the most advantageous risk-benefit treatment for neurotic depression.
- Acute antidepressant medication treatment should focus on multiple full, fair trials of antidepressant medications from different classes.
- Polypharmacy with antidepressants does not reliably achieve remission; care should be taken to avoid excessive antidepressant treatment if clear benefits are not accruing, given the added side-effect burden of polypharmacy.

The approach to using psychotherapies versus medications in unipolar depression is complex. In this chapter I will provide a summary of my view on this approach.

EFFICACY OF PSYCHOTHERAPIES

Cognitive behavioral (CBT) and interpersonal therapies (IPT) have been proven effective in unipolar depression (see Chapter 22). Since CBT and IPT have been standardized and manualized, they are amenable to empirical research and have been well studied for the treatment of mood disorders. Yet a certain amount of controversy and inconsistency surrounds the results of those empirical studies. Some studies have found that the psychotherapies are as effective as antidepressant medications; others have not. Some have found the psychotherapies useful as adjuncts to medications; others have not. Some researchers have concluded that psychotherapies are as useful as antidepressants; others have not. How can we make sense of this research?

Frequently, findings that appear to be contradictory when summarized in an abstract do not conflict at all when the methods of those studies are compared carefully. I would agree with two key conclusions drawn by some investigators of this literature. First, in the studies in which psychotherapies were equally effective or more so as antidepressant medications, most patients were being treated in their first or second episode of major depression. Second, in the studies in which antidepressant medications were more effective than psychotherapies, patients generally had experienced three or more episodes. You will recall that about a third of patients with unipolar depression have only a single episode, and two-thirds have recurrent episodes (usually more than three). I discussed previously that Kraepelin had long differentiated between these two kinds of illnesses, recurrent and nonrecurrent affective illnesses. He considered them to be different diseases. Thus we might translate the research evidence into the statement that psychotherapies appear particularly effective in

nonrecurrent unipolar depression (first or second episode) but not in recurrent unipolar depression (three or more episodes).

TIP

It is important to quantify the number of major depressive episodes experienced by a depressed patient because this fact is key in choosing between psychotherapy and medication treatment.

Recurrence also might be viewed as a proxy for severity. Indeed, most literature indicates that patients with more severe depressive symptoms in an episode (higher depression rating scale scores) respond better to antidepressant medications than to psychotherapies alone. However, interestingly, there is accumulating evidence that such severely depressed patients (especially those with melancholic features) respond even better to augmentation of antidepressant medications with psychotherapies. Thus antidepressants are necessary for the treatment of severe or recurrent depression but may not be sufficient, whereas psychotherapies are not necessary but may provide additive benefit when used as an adjunct to antidepressant medications. On the other hand, in less severe and nonrecurrent depression, psychotherapies alone may be sufficient for acute treatment.

Long-term treatment with psychotherapies may be unnecessary in persons with nonrecurrent depression, almost by definition. In recurrent depression, long-term treatment (more than 5 years has been proven empirically) is needed with antidepressant medications, whereas long-term use of psychotherapies may or may not prove useful. If antidepressants are discontinued in patients with recurrent unipolar depression, relapse is almost guaranteed.

Based on these studies, I can make recommendations for the use of psychotherapies or antidepressant medications in the treatment of unipolar depression (Table 8.1).

CLINICAL VIGNETTE

The patient is a 27-year-old man who has had no psychiatric symptoms until being markedly depressed after his recent divorce. He wishes to avoid medications and agrees to 4 months of weekly CBT. He improves gradually and remains well at 2-year follow-up.

TABLE 8.1. Rules for the Treatment of Acute Unipolar Depression

Type of Unipolar Depression	*Treatment Options*	*Duration of Treatment*
Nonrecurrent	Medication alone or psychotherapies alone	6–12 months
Recurrent	Medication often required. Psychotherapies as adjunct	Medication often indefinitely, sometimes short term Psychotherapies as needed
Neurotic depression	Psychotherapy often best option Medication as adjunct or alone if psychotherapy not feasible	Psychotherapies sometimes indefinitely, usually long term Medications sometimes indefinitely, preferably short term

Note: Nonrecurrent unipolar depression refers to the first or second major depressive episode; recurrent depression refers to three or more episodes. Psychotherapies refer to CBT and IPT in the case of episodic depression; no specific psychotherapies have been proven or disproven in neurotic depression.

ANTIDEPRESSANT EFFICACY

Antidepressants, if effective, generally need to be continued in recurrent unipolar depression. However, a different question to ask is, "How frequently are antidepressants effective in treating acute depression?" To answer this question, I now have empirical data, unavailable for the previous edition, based on the huge National Institute of Mental Health (NIMH)–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study (Figure 8.1).

TIP

About 50% of depressed patients respond after three trials of medications; many of the remaining 50% likely have bipolar disorder.

I strongly advise that the remaining 50% be carefully assessed for bipolar depression, the most common misdiagnosis leading

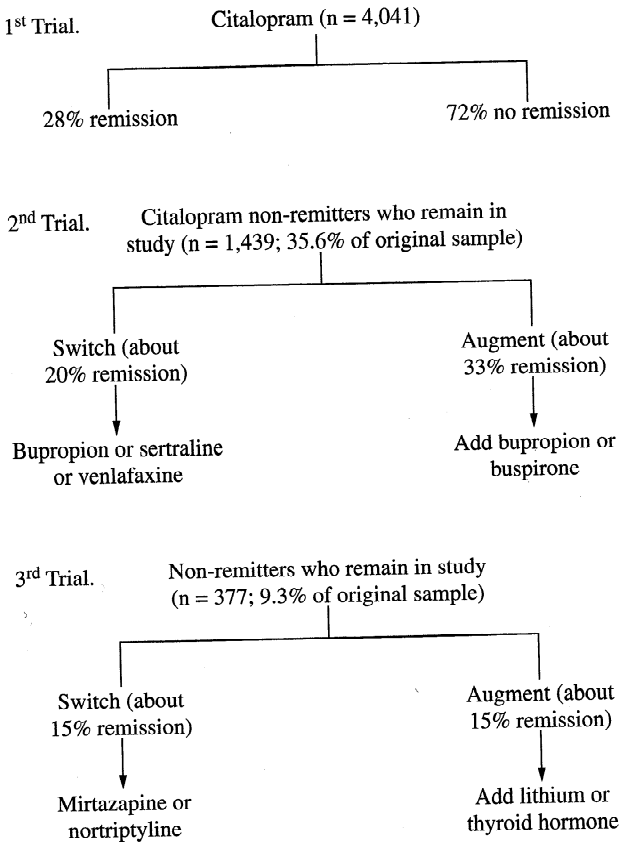

FIG. 8.1. Response rates to acute antidepressant trials. The Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study. Each trial is 12 weeks long. Overall, about 30% of patients responded after the first open trial, and then another 30% responded after switching to another agent or augmentation with another agent. The cumulative remission rate after the first two phases was 53% for those who remained in the study. However, many patients either did not tolerate the medications owing to side effects or dropped out of the study for other reasons. See Chapter 12 for further discussion of STAR-D.

to antidepressant nonresponse. New data indicate that one-half of treatment-refractory unipolar depressed patients appear to have bipolar depression and respond to the addition of mood stabilizers (or sometimes the use of mood stabilizers alone; see Chapter 18 for further details). The other half (half of 50%, or 25% of the total sample) has pure refractory unipolar depression. I strongly suggest that these patients receive trials of tricyclic antidepressants (TCAs) first, followed by monoamine oxidase inhibitors (MAOIs) and/or electroconvulsive therapy (ECT). In practice, most of these patients are no longer offered, nor do they accept, any of these highly effective options.

What constitutes a full, fair trial of antidepressant? Opinions on this subject have varied over the last decade. For unipolar depression, the following rules generally are accepted:

1. The minimum duration of an effective trial is 4 weeks for most antidepressants, but 8 weeks is ideal.
2. The minimum effective dose of each antidepressant should be reached.
3. Patient noncompliance must be ruled out.

There are some nuances to these rules. For instance, of all antidepressants, fluoxetine has a longer minimum duration of treatment than laid out in rule 1; because fluoxetine has an extremely long half-life, it requires at least 6 weeks for a full trial, with 12 weeks being ideal. Amphetamine antidepressants, on the other hand, may be effective in 1 week, with 4 weeks being ideal.

CLINICAL VIGNETTE

The patient is a 35-year-old woman who has had two previous major depressive episodes at ages 22 and 28. Her current major depressive episode has lasted 5 months. All her depressions were associated with school-related stresses because she has taken strenuous courses in college and graduate school and is currently undergoing significant difficulty in finding her first faculty position after obtaining her PhD. Her physician recommends medication treatment with an antidepressant, which she accepts. She responds well and is maintained on the antidepressant and is still doing well 3 years later despite the demands of a busy faculty position at a major university.

TABLE 8.2. Stages of Treatment Resistance

Stage I	Nonresponse to a full trial of an antidepressant
Stage II	Nonresponse to at least two full trials of antidepressants, one of which is from a different class
Stage III	Nonresponse to at least two full trials of antidepressants, one of which is a TCA
Stage IV	Nonresponse to at least three full trials of antidepressants, one of which is MAOI
Stage V	Nonresponse to at least three full trials of antidepressants, one of which is an MAOI, and nonresponse to ECT

The definition of treatment-refractory depression has varied based on these descriptions of full antidepressant trials. At a minimum level, failure to respond to one full antidepressant trial will identify a refractory population. However, as the preceding figure suggests, failure to respond to two or three trials seems to identify an increasingly unresponsive depressed population. Thus most strict definitions require failure to respond to three full antidepressant trials. Furthermore, sometimes a person will not respond to multiple antidepressants of a particular class (e.g., serotonin reuptake inhibitors) but will respond to the first antidepressant tried in a different class (e.g., noradrenergic agents such as TCAs). Thus alternative definitions have been suggested that incorporate the concept of attempting trials with different classes of antidepressants with alternative mechanisms of action. A recent proposal that seems clinically useful to me is summarized in Table 8.2. This table is particularly useful because it stages levels of treatment resistance in accordance with evidence that TCAs, MAOIs, and ECT (in that order) are the most effective antidepressant treatments.

Given that many patients today do not receive a full, fair trial of TCAs, MAOIs, or ECT, most would not reach beyond stage II treatment resistance. This would flag the clinician to realize that these patients are still potentially responsive if appropriate treatments are offered.

REMISSION OR RESPONSE?

Recently, a great deal of attention has been paid to the fact that even though 50% of patients respond acutely to antidepressants, a smaller number (perhaps around 20% to 30%) recover

normal functioning. In other words, while a person may no longer be clinically depressed, he or she may not resume his or her normal jobs, routines, and social relationships. Despite the availability of more adequate treatment, depression remains among the top causes of morbidity and mortality worldwide, according to international epidemiologic studies. Why is this the case?

One reason appears to be that treatment response is not the same as treatment remission. In antidepressant studies, *treatment response* is defined as 50% or more reduction in depression rating scale scores. This is the kind of improvement that is notable qualitatively in standard clinical treatment. However, a patient may continue to experience 40% or 30% or 20% of symptoms. We call this phenomenon *residual depression*. Some studies suggest that individuals with residual depression experience the most impairment in their functioning.

Treatment remission is defined as almost complete absence of symptoms, to 10% or less of the original burden. Such individuals, as a rule, recover normal functioning. Even though acutely it is quite acceptable to achieve treatment response with 50% or more benefit in symptoms, in the long run, remission should be the goal. In other words, if the patient responds initially but then has residual symptoms, the clinician should not be satisfied and should continue to seek means of removing those residual symptoms. This may involve a change in medication or adjunctive psychotherapies. However, frequent changes in medications often leave patients confused and doctors frustrated. Often medications are simply added one on top of the other, leading to a poly- pharmacy that increases side effects, decreases quality of life, and often ends in patients dropping out of treatment.

I often tell patients that, unfortunately, our medications—antidepressants and mood stabilizers both—are like sledgehammers; if you are severely depressed or manic, they can improve your mood, removing the most severe symptoms, but they do not always leave you completely normal, right in the middle of the mood spectrum. Often patients are left slightly depressed, yet adding more antidepressants or other medications does not seem to easily solve that problem. What we need, then, is a tuning fork instead of a sledge hammer. We still do not know how to achieve remission successfully in such persons. My hunch is that perhaps adequately chosen and proven psychotherapies might play an important role in improving such residual depression, but there are as yet limited

data in this regard, as well as practical resistance on the part of patients (e.g., time, expense) and corporate America (e.g., the refusal of insurance companies to pay for such psychotherapies long term and the incentives of pharmaceutical companies to promote medications instead). This goal in the treatment of depression remains elusive.

LONG-TERM TREATMENT WITH ANTIDEPRESSANTS IN UNIPOLAR DEPRESSION

It should be acknowledged that long-term treatment with antidepressants is less well established than short-term efficacy. Meta-analyses of over 10 long-term trials with new antidepressants have been published, supporting efficacy; however, most of these studies are only 1 year in duration with serotonin reuptake inhibitors (SRIs) and other new antidepressants. Longer-term treatment is being conducted with hardly any evidence base. Further, it is quite clear that the pharmaceutical industry generally has not published negative studies, some of which may never have even been made public in any setting. Thus we cannot be sure that the available meta-analyses, based on published studies, are valid because they may have excluded unpublished studies. Lastly, some studies suggest an absence of long-term benefit with antidepressants. For instance, in one study from Italy, randomized transfer of 80 patients from antidepressant treatment to CBT with 4- to 10-year follow-up indicated that those who continued on antidepressants did worse than those who switched to CBT.

It is also often noted that antidepressant discontinuation after long-term treatment in unipolar depression leads to rapid depressive relapse, often viewed as evidence of long-term efficacy and the need for continued antidepressant treatment. An alternative explanation is the occurrence of a withdrawal syndrome, which would argue for even earlier antidepressant discontinuation to avoid the development of tolerance and withdrawal.

I am not certain where this debate will end. It seems reasonable at this point for clinicians to be open to the limited nature of our evidence base for long-term efficacy with antidepressants. Perhaps the most rational conclusion currently would be that some patients may need long-term antidepressant treatment, and others may not; both clinicians and patients should be open to both possibilities.

THE PHENOMENON OF NEUROTIC DEPRESSION

As noted in Chapter 2, the term *neurotic depression* was removed from the official DSM-III lexicon in 1980, replaced with the heftier sounding *generalized anxiety disorder* (GAD) and *dysthymia*. Consequently, clinicians frequently see patients with the comorbidity of GAD and dysthymia, which likely represents the same class of patients that used to be labeled as having *neurotic depression* before 1980. I have returned to the term *neurotic depression* because I think it more clearly captures the symptoms experienced by these patients without pseudoscientific jargon. *What is central to this syndrome is chronic moderate anxiety and depressive symptoms that do not meet criteria for a major depressive episode most of the time.* These patients do not have recurrent discrete major depressive episodes separated by periods of relatively normal functioning, and their anxiety symptoms are equally disabling as their mood symptoms.

When treating neurotic depression (GAD/dysthymia), clinicians often use the same approach as in the treatment of recurrent unipolar depression, that is, long-term antidepressant treatment. This is partly because the DSM-IV labels all these syndromes *major depressive disorder* (adding comorbidities for some patients with dysthymia and GAD). In my view, the conflation of these conditions diagnostically leads to unproven and possibly unnecessary treatments. Long-term benefits with antidepressants are far from established in GAD and dysthymia; short-term efficacy makes little sense in these chronic conditions. Yet it seems to me quite unscientific, and in fact, anti-Hippocratic, to commit patients to long-term antidepressant treatment with the associated costs and side effects in the face of unknown efficacy. Despite my own past skepticism, I now think that perhaps the old psychoanalysts had it right: Such patients probably should be treated with psychotherapies, which at least will not harm them and often do appear to help them. Obviously, there are costs to the psychotherapies, both in dollars and in time, often not reimbursed by insurance companies, and no pharmaceutical companies engage in marketing for the psychotherapies. But putting aside the widely acknowledged inadequacies of our health care system, strictly from the scientific point of view, my perspective is that the psychotherapies are to be preferred to routine long-term antidepressant treatment in such patients.

CLINICAL VIGNETTE

A 38-year-old man complained of chronic anxiety, insomnia, worrying all the time, gastrointestinal upset, headaches, chronic depressed mood, general amotivation (although preserved for some hobbies), low self-esteem, and difficulty with concentration. He denied guilt or suicidal ideation. His energy level fluctuated, sometimes being near normal and sometimes being low, but not constantly severely low. His general state of anxiety and depression had led to numerous problems in relationships and poor progress in his profession. He had never made any suicide attempts or been hospitalized and had not sought medications or psychiatric attention previously. Under careful interview with him and a phone call to his mother, the interviewer was not able to elicit a history of repeated episodes that were worse than his chronic moderately depressed/anxiety condition. One or two possible periods of increased depression lasting 3 months each were elicited in his teens and early twenties, but otherwise, the history obtained was of a chronic nature. The patient was ambivalent about psychotherapy, saying that he did not have the time or money for it because his insurance would cover only 10 sessions. The psychiatrist thus prescribed sertraline, titrated to 200 mg per day, for 3 months; the patient felt only slightly better and complained of sexual dysfunction. Bupropion led to no benefit after 2 months of treatment at 400 mg per day. Venlafaxine led to heart palpitations after 1 week; citalopram at 40 mg per day for 3 months helped anxiety moderately but did not improve his depression. Combination of bupropion plus citalopram led to no further benefit and caused worsened insomnia. Finally, the psychiatrist informed the patient that he had treatment-refractory depression. The diagnostic interview was repeated, with his mother's presence, and the same history was confirmed. The psychiatrist now strongly recommended the addition of psychotherapy. The patient agreed to see a social work colleague of the psychiatrist at a reduced fee. After 3 months of psychotherapy, the patient felt mildly better; after 6 months, the patient felt moderately less anxious; and by 1 year, the patient's symptoms had improved at least moderately for both anxiety and depression. At that point his psychiatrist tapered off citalopram, the only remaining antidepressant, with no worsening of the patient's condition. The patient remained in long-term psychotherapy, reduced in frequency after 1 year to once monthly.

SUMMARY

There are two basic phases in the treatment of unipolar depression: the acute phase and the prophylaxis phase. In the acute phase, the most important objective is to use full, fair trials of antidepressants, moving from one class to another. In the prophylaxis phase, antidepressants may be less effective. Psychotherapies are most effective in acute-phase treatment of nonrecurrent unipolar depression. Further, attention should be paid to residual depressive symptoms because they are associated with impaired functioning. Remission, rather than response, is the goal of treatment and may be the best rationale for combined pharmacology-psychotherapy treatment.