Pharmacologic Considerations in Treating Depression: A Patient-Centered Approach

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ABSTRACT

OBJECTIVE: To review the tricyclic antidepressants, selective serotonin reuptake inhibitors, and dually acting antidepressants and their economic and treatment implications.

SUMMARY: Major depressive disorder’s cost to the U.S. economy is staggering, but the selection of drugs available to treat it has expanded to include drugs that have better side-effect profiles. Regardless, remission rates are high, and, often, patients are not treated aggressively enough. Somatic presentations are more common than previously thought, and pain, in particular, may be associated with depression. Pain and depression are both regulated by serotonin and norepinephrine, and several studies suggest that using dual-action antidepressants may be helpful in patients who have an element of pain to their disorder. Titration to an adequate dose of any antidepressant is important, as is sustaining treatment for months to years, depending on the patient’s history.

CONCLUSION: Increasingly, the mental health community is realizing that the goal of treatment for patients with major depressive disorder must be sustained remission.

KEYWORDS: Serotonin reuptake inhibitors, Suicide, Major depressive episode, Somatic symptoms, Dually acting antidepressants

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In the early 1980s, the U.S. Department of Defense (DoD) established the Tri-Service PharmacoEconomic Council at Fort Sam Houston, Texas, comparing the use of tricyclic antidepressants (TCAs) with the new generation of selective serotonin reuptake inhibitors (SSRIs) as one of the first efforts at establishing cost-effective treatment options for major depressive disorder (MDD) for the DoD. These 2 categories were specifically selected to study (among others) because of the dramatic differences in pharmacy costs between TCAs and SSRIs. The study’s mission was to determine if one class should be considered first-line treatment. The PharmacoEconomic Council determined that using TCAs cost about twice as much overall as SSRIs, although the pharmacy costs were certainly much higher for SSRIs.

These particular studies did not consider lost productivity or absenteeism. Instead, they looked at actual raw costs: the cost of intensive care unit stays after accidental or deliberate overdoses and emergency department visits for side effects and complaints like constipation, urinary retention, fainting spells, etc. The eventual summary DoD guidelines designated SSRIs as first-line treatment. This article endeavors to take the reader through a patient-centered-care approach for understanding how psychiatrists select antidepressants. It will cover the importance of identifying depression’s somatic symptoms and pursuing remission. It is no longer acceptable for patients to get better; they must get completely well.

Epidemiology of Depression

One of every 6 people (17%) in the United States will suffer from an MDD episode during their lives. Patients who required hospitalization for MDD have up to a 35% lifetime risk for suicide. Depression’s total annual cost to society is approximately $44 billion in direct costs, with an additional $55 billion in lost productivity.

People who experience depression are much more likely to develop other serious medical problems. In patients with serious medical problems who consequently develop depression, the problems of stress, morbidity, and mortality increase significantly.

The Journal of the American Medical Association published a landmark article elucidating morbidity and mortality issues in 1993. The researchers evaluated 222 patients who had first-occurrence myocardial infarctions (MI) using the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for major depressive episode. After interviewing patients 5 to 15 days after an MI, researchers followed the patients for 6 months. They then divided those patients with depression into 2 groups—those who were treated with antidepressants for their symptoms and those who were not. Age varied, and the sample was 78% male. At 6-month follow-up assessment, 12 patients had died, all from cardiac causes. Depression significantly predicted mortality after control for various confounding factors. Patients who became
Depressed following an MI but were untreated had a 5-fold increase in mortality compared with people who were treated for their depression. The researchers concluded that “major depression in patients hospitalized following an MI is an independent risk factor for mortality at 6 months. Its impact is at least equivalent to that of left-ventricular dysfunction and history of previous MI. Additional study is needed to determine whether treatment of depression can influence post-MI survival and to assess possible underlying mechanisms.”

The results of the study were quite controversial. Why? The study’s small sample size, limited university setting, and short duration raised questions. The findings implied that some morbidity and mortality in post-MI patients had little to do with medical interventions. Essentially, the study identified health decline as depression’s sequel in post-MI patients.

A follow-up study, commissioned by the National Institutes of Health and the American Heart Association, was published in the journal Circulation in 1995. This longer study expanded the parameters involved to multiple centers across the country and significantly more patients. After 18 months, the study was halted because at 6 months, 12 months, and 18 months, the study investigators affirmed the previous study’s findings. Patients experiencing depression following an MI who were untreated had a significantly greater increase in mortality.

Treating Depression

Depression is a very treatable mental illness. However, with the advent of fluoxetine, sertraline, paroxetine, venlafaxine, bupropion, mirtazapine, citalopram, and all the other antidepressants introduced in the last 15 years, and with the logarithmic increase in the number of prescriptions written for patients with depression, the incidence of suicide in the United States is still higher than is acceptable. Historically, we believed that compliance problems with monoamine oxidase inhibitors (MOAIs) and TCAs led to substantial numbers of treatment failures; enhancing compliance might impact the suicide rate. Clinicians applauded the arrival of the new generation of antidepressants. Because their side-effect profiles were superior, a dramatic decline in the incidence of suicide in the United States was anticipated over the next 5 to 10 years. A significant decline did occur, but not to the extent clinicians had hoped.

This is a multifactorial problem, and solutions must also be multifactorial. Barriers and stigma dissuade people from taking antidepressants even if they seek treatment. And, even with better-tolerated agents, the average length of time that patients remain on a prescribed SSRI is in the range of 6 to 8 weeks. At least 20%—and perhaps higher percentages—of patients never even have their prescription filled. Yet, patients with first episode MDD should stay on medication for a minimum of 6 to 9 months, with the average being 9 to 12 months.

It appears that patients visit primary care physicians more readily than they visit psychiatrists, and primary care physicians seem to be more accessible to diagnose depression and prescribe antidepressant medication. But, because patients either fail to visit the pharmacy or eventually discontinue their medications prematurely, our impact on the suicide rate is unacceptable.

Many patients remain undiagnosed, but even if they are diagnosed, some may be inadequately treated. Only a third of patients achieve real remission. Busy clinicians, overwhelmed by the volume of patients they must see, may not be able to follow up to ensure patients are achieving a therapeutic response.

Psychiatrists generally move patients into the therapeutic range quickly, but many primary care physicians don’t have the time or may not have the knowledge to know that higher doses of particular medications have a greater chance of treatment success. Overall, 30% to 45% of treated depressed patients will show partial response or no response at all. Remission failure is associated with increased relapse risk. One current drawback: available antidepressants take 2 to 4 weeks for significant symptom relief.

It would be ideal if the next generation of antidepressants could help patients by the end of the first week. By definition, remission rarely occurs at the end of the first 2 to 4 weeks; it probably takes longer than that. By the same token, one reason people commit suicide is because they actually seek care and get help. When diagnosed, they may be started on the right antidepressant medication for them; however, in the next 2 weeks, they are actually at the greatest risk for suicide.

Why is this? Once patients are on antidepressants, their energy level increases, followed somewhat later by a heightened sense of hope. Initially, patients may feel overwhelmed by the things that have happened as a consequence of depression. So for patients who are hopeless, tearful, have not slept well for weeks or months,
and feel desperate and who are then given an antidepressant, it is not the 2 weeks before initiation of treatment that represent the greatest chance of that person harming themselves. It is actually the next 2 weeks, when the patient is energized that the person can mobilize his or her hopelessness and despair and act on it.

## Somatic Presentation

Organized medicine has focused on depression’s emotional symptoms. An old joke goes something like this: Psychiatrists only worry about problems from the neck up. But, secondary physical complaints that probably accompany depression in many populations may be more important than sadness, hopelessness, worthlessness, or guilt. Consider, for instance, that about 16% of antidepressants are prescribed by nonpsychiatrist medical specialists (i.e., primary care physicians, nurse practitioners, etc.). Our colleagues who are not psychiatrists must acknowledge and address these secondary physical symptoms, as must psychiatric specialists.

One study reviewed 1,000 adult clinic patients, selected both randomly and by convenience and screened for the presence or absence of 15 common physical symptoms and whether symptoms were somatoform (i.e., lacked an adequate physical explanation). Each of the 15 common symptoms was frequently somatoform. Patients with any physical symptom were more than 2 to 3 times more likely to have a diagnosis of a mood or anxiety disorder. As the number of physical symptoms increased, so did the likelihood of a psychiatric disorder. The prevalence of a mood disorder in patients with 0 to 1, 2 to 3, 4 to 5, 6 to 8, and 9 or more symptoms was 2%, 12%, 23%, 44%, and 60%, respectively, and the prevalence of an anxiety disorder was 1%, 7%, 13%, 30%, and 48%, respectively. Notable functional impairment also increased significantly with physical symptoms of depression. Thus, multiple or unexplained symptoms may signify a potentially treatable mood or anxiety disorder.

A second study, conducted 6 years later, confirmed these findings. Based on findings that suggested that depressed patients in non-Western countries are more likely to report somatic symptoms than are patients in Western countries, these researchers used data from the World Health Organization’s study of psychological problems in general health care to examine the relation between somatic symptoms and depression. Conducted in 1991 and 1992, the study examined 25,916 patients in 14 countries. Of these patients, 5,447 agreed to a structured assessment of depressive and somatoform disorders. Approximately 10% (N = 1,146) of patients met the criteria for major depression (Figure 1). A full half of depressed patients reported multiple unexplained somatic symptoms; 11% denied depressive symptoms when questioned. Their proportions were consistent among the 15 centers. Thus, somatic symptoms associated with depression are common in many countries. The frequency of somatic presentation varies greatly and may reflect clinician or system characteristics or cultural differences among patients.

Interestingly enough, patients who seek psychiatric care are not necessarily the highest medical services users. Patients who are not ready—or able—to acknowledge they have an emotional condition, but suffer from the physical symptoms of depression, will return repeatedly to their primary care physicians and utilize medical resources heavily. Patients with chief complaints of pain are high medical resource utilizers.

NIMH studies have shown that patients with moderate to severe depression are more likely to have poor outcomes without medication than the patient receiving psychotherapy alone. So what is psychotherapy counseling’s role in mental health? It is probably most applicable to people who have mild to moderate or nonsevere, nonacute depression; this form of depression is more prevalent. But for the patient with the less common moderate to severe depression, combining counseling with psycho-pharmacologic management consistently provides the best outcome.

The Diagnostic and Statistical Manual of Mental Disorders classification for depression focuses primarily on emotional symptoms, with less emphasis on physical symptoms. Figure 2 depicts the central nervous system (CNS). In patients who have painful physical symptoms of depression, ascending and descending pain pathways are critical for pain perception. CNS imbalances of serotonin (5-HT) and norepinephrine (NE) may cause concurrent 5-HT and NE imbalances in the spinal cord. Serotonin and NE are key modulatory nerve transmitters in the descending inhibitory pathway and may actually reduce patients’ sensation of pain.

**FIGURE 2** Emotional and Painful Physical Symptoms: A Shared Neurochemical Link in Depression?

- Abnormalities of 5-HT and NE are strongly associated with depression.
- Limbic system modulates pain perception.
- 5-HT and NE are key modulatory neurotransmitters in the descending inhibitory pathway and are part of the body’s endogenous analgesic system.

*5-HT = serotonin. NE = norepinephrine.*

These neurotransmitters are also critical in the ascending pathway in terms of how the pain message from upper or lower extremities, (i.e., low back pain, pelvic pain) is actually transmitted to the CNS. Serotonin and NE imbalances may enhance pain perception.13,14

Silverstein, using data from the Epidemiologic Catchment Area (ECA) study, divided patients into the following groups: (1) those who met criteria for major depression and had appetite and sleep disturbances and fatigue (somatic depression) and (2) those who met depression criteria but were somatic symptom-free (pure emotional depression). He found that the prevalence of somatic depression was much higher among women and that somatic depression was more likely to be associated with higher rates of pain. In women, significantly higher rates of anxiety disorders and chronic dysphoria were also seen.15,16

Patients, when asked why they were referred to a psychiatrist, often answer “Because I am nervous.” Nervousness is not a diagnosis; it is a symptom. Ethnicity and culture will affect the meaning of “nervousness.” Nervousness may be anxiety, tremulousness, insomnia, weakness, or fatigue.

Antidepressants and Pain Treatment

Researchers identified the TCAs as preferred treatment for patients with chronic pain syndromes almost 30 years ago because TCAs potentiate both 5-HT and NE in the CNS. Today, physicians in all specialties use them for medical conditions such as migraine headaches, low back pain, fibromyalgia, and peripheral neuropathy. Often, physicians employ a cocktail of different medications for patients with severe unrelenting pain, few of whom respond to monotherapy.17 SSRIs, however, are not usually effective for patients with pain, unless they are combined with other agents.18,19 Polypharmacy can be costly. Agents with dual 5-HT- and NE activity, like the TCAs, appear to benefit pain patients more consistently than single-action antidepressants. Therefore, pain-free patients may be good candidates for an appropriate first-line choice of a generic SSRI. Using a patient-centered approach, patients who report an element of physical or painful symptoms, or perhaps with impulse control, aggression, appetite, and sexual functioning.

When patients have depression with concurrent painful physical symptoms, achieving remission is critical.20 The degree of physical symptom improvement correlates with the ability to achieve remission. This select group of patients will need to be treated with an agent that affects both 5-HT and NE (e.g., not an SSRI) in order to help them manage their physical symptoms or the achievement of remission will be unlikely.

Paykel and colleagues found that more than 90% of patients with residual symptoms of depression who responded to antidepressant therapy (but did not achieve remission) had mild to moderate general somatic symptoms.6 Somatic symptoms include fatigue, gastrointestinal complaints, pain, and other physical manifestations of the depression. These findings, confirmed in a second study, found that depressed patients were most likely to report or have “musculoskeletal diseases.”21 With remission, which has become the goal of treatment for patients with MDD, if patients did not become completely better, the majority suffered from ongoing painful, physical symptoms.

What links dual-acting antidepressants and pain? Again, antidepressants that increase both 5-HT and NE also impact both depression and some pain syndromes—with or without depression. It is useful to note that many of the indications for which we use antidepressants are not U.S. Food and Drug Administration-approved, including conditions such as fibromyalgia, for which there are no FDA-approved treatments or evidence of efficacy.

The ultimate goal in treating depression is to achieve complete symptom remission.22 Settling for a partial response can have disturbing consequences: increased likelihood of relapse and increased risk of treatment resistance.23 In summary, many depressed patients are likely to present with both emotional and associated physical symptoms. In the treatment of depression, unmet needs include addressing not only emotional symptoms but also treating the physical symptoms. The goals of successful treatment include achieving remission and symptom relief as rapidly as possible.

Neurotransmitters: Current Scientific Thinking

In the CNS, the Raphe nuclei in the lower part of the brain are the densest concentration of 5-HT-producing neurons within the upper CNS. People who have inadequately functioning Raphe nuclei are 5-HT-deficient. The locus coeruleus is the primary source of NE-producing neurons in the CNS. The CNS has both 5-HT and NE projections ascending into the prefrontal cortex and the cerebral hemispheres of the brain. The very prominent downward projections of these nuclei into the spinal column, however, have been neglected. Recall the spinal cords ascending and descending pathways (Figure 2). These downward projections must have adequate systems of 5-HT and NE, particularly for depressed individuals suffering from painful physical symptoms.24

Serotonin and NE have definite functional domains. Insufficient NE leads to disorders of vigilance and motivation—patients who may be amotivational, lack energy, communicate poorly, and so forth and, therefore, might be good candidates for a medication like bupropion, which has strong dopamine and NE-promoting properties. Serotonin deficits tend to cause problems with impulse control, aggression, appetite, and sexual functioning. So, patients who are impulsive, aggressive, and lack sexual energy or interest may respond to a 5-HT-enhancing medication.25-28

Serotonin’s and NE’s domains also overlap, and symptoms of anxiety, irritability, pain, cognitive function, mood, and emotion result in this area of overlap. Unfortunately, it is impossible to determine, based on clinical interview alone, if patients are suffering from a 5-HT, NE, or dopamine deficiency.

Two Danish University Antidepressant Group studies compared the TCA clomipramine with citalopram and then paroxetine. In both studies, clomipramine was found more efficacious than the SSRI. It is possible that antidepressants that incorporate...
both 5-HT and NE reuptake inhibition may have a broader spectrum of action and prove to be more effective.29-31 These studies, though small and reliant on the 17-item Hamilton Depression Rating Scale (HAM-D17) tool, suggest that dual-action antidepressants may offer an increased likelihood of treatment success in achieving remission.

### Unmet Needs

Patients can respond to treatment without achieving full remission. Depression studies before about 1997 or 1998 considered achieving a 50% symptom reduction (as measured by the HAM-D17 score) adequate. An interesting analogy comes to mind involving cancer: Would an oncologist or cancer patient be happy with eradication of 50% of a tumor? In oncology, the treatment goal is total eradication of tumor cells for 5 years before establishing successful remission. Other medical specialties might also consider more ambitious goals such as this.

Realistically, all patients with major depression will not achieve 100% remission. For patients who comply with treatment, our goal (and the primary care physician’s goal) should be to choose an antidepressant medication that has the potential to achieve the therapeutic dose during the first days of treatment. Additionally, it should be tolerable so that patients stay on the medicine long enough to achieve remission.

Research criteria still define antidepressant response as a 50% reduction in symptoms from the baseline HAM-D17 score. One observed outcome of the Paykel study in 1995 was the following: Depressed patients with residual symptoms who were treated for depression and did not achieve complete symptom resolution had a greater risk of relapse. In fact, 76% relapsed. Paykel determined that more than 90% of study participants had mild to moderate somatic symptoms. Patients treated to the point of remission, however, only relapsed at a rate of 25%. The long-term outcome of achieving remission was much more favorable.

Paykel defined remission as minimal or no symptoms of depression and, more importantly, a return to normal psychosocial functioning. In general, depressed patients are not concerned with research definitions; they want to know if and when they will be better. They define “better” as feeling better, sleeping well, eating normally, improved concentration, and functioning well at work and home. They want effectiveness in the real world, not clinical research trial efficacy.

Many scales are often used (including the BECK, IAS, and Madras), but the HAM-D17 may be appropriate for both research and office use. Figure 3 depicts the HAM-D17, with a score of 7 or less defined as virtually complete symptom resolution. Scores of 15 or greater constitute ongoing symptoms of depression. So, if a patient enrolled in a clinical trial had scored 30 and treatment reduces the Ham-D17 total score to 15, it is likely that the patient will be pleased with the improvement. The patient will probably no longer be suicidal or tearful and may, in fact, be hopeful. Perhaps in an effort to please the physician, he or she will report feeling better. In response, the physician will reduce the current dose of medication even though the patient has not achieved remission and, therefore, it is not therapeutically appropriate to persist at this dose of the medicine. Using a depression measurement instrument, however, helps physicians assess actual improvement in functioning and directs dose modifications toward the achievement of remission. Those who disagree would indicate that the HAM-D fails to quantify reverse neurovegetative symptoms and is biased to sedating antidepressants.

This is an essential message to impart to primary care physicians. Although many are comfortable with quantifiable medical measurements like cholesterol levels, they seem to shun the psychiatric research diagnostic instruments. Ancillary personnel can, however, be trained to administer these instruments. Short of using an instrument, there is virtually no way to measure complete symptom remission.

A depressed patient’s clinical progression after diagnosis and treatment can be described using the 5 Rs: response, remission, relapse, recovery, and recurrence. Once diagnosed and treated, it is hoped that patients begin to respond. They may steadily improve to remission or recovery, or, at any time, they may relapse. Depression is not an illness that affects most people only once and never recurs. Depression is often a chronic, unrelenting medical illness that takes lives. The chance of recurrence following a first episode of depression is about 50%. After 2 episodes of depression, the chance of future episodes increases to about 70%. And after 3 distinct episodes of depression, the chance of recurrence exceeds 90%.

Many practicing psychiatrists have indicated that length of treatment should follow the following paradigm: Treat a first episode depression for about 9 months. (Many psychiatrists never stop an antidepressant in the winter months, as the risk of relapse for patients prone to developing seasonal affective disorder is too great.) For a second episode of depression, treatment for 2 to
3 years is prudent. A third (or more) episode(s) of depression reasonably invites treatment for 5 years to life. Only complete remission appears to reduce the incidence of suicide.

The idea of remission in depression is exactly like the concept of remission in any other medical illness. In 1998, Miller and colleagues examined this issue of the significant impairment many chronically depressed patients experience. The researchers compared sertraline and imipramine after patients with chronic depression were treated for 12 weeks. They examined the subjects’ psychosocial functioning data before and after treatment with normative data available from community samples. They found that treatment with sertraline or imipramine improved psychosocial functioning significantly, and these improvements were noted fairly early—at week 4. But despite early improvements in functioning, participants did not reach levels of psychosocial functioning similar to the nondepressed community sample unless they achieved full symptomatic response (remission) during acute treatment.32 These findings underscore the importance of achieving remission.

Treatment-resistant depression may account for up to 30% of patients diagnosed with depression. These patients may take 1 antidepressant for 3 or 4 months, then another for 3 or 4 months, until they have tried multiple antidepressants with limited benefit. Monitoring reports may indicate that this patient is a very high utilizer of medical resources.33,34 Often, polypharmacy is necessary with a dual-action antidepressant (perhaps extended-release venlafaxine) and/or an augmenting agent like bupropion, and/or a mood stabilizer like lamotrigine. The potential consequences of failing to achieve remission are summarized in Table 1.

### Limitations of Current Dual-Acting Antidepressants

Currently, only the TCAs and venlafaxine possess the dual action needed for optimal remission. Nevertheless, they have multiple limitations. The TCAs are associated with cardiotoxicity, orthostasis, anticholinergic effects, weight gain, and sedation. Accidental dose changes (i.e., forgetting and taking medication twice) can lead to prolonged QT interval on electrocardiogram or sudden death in patients with arrhythmia. Orthostasis (impaired ability to adjust to positional changes) is a serious concern, particularly in the elderly. It can lead to falls and fractures, complicating care. Anticholinergic side effects can cause noncompliance, as does weight gain and profound sedation, which is why dosing at bedtime is preferred.

Venlafaxine requires high doses to balance available 5-HT and NE reuptake inhibition. At 75 mg a day, venlafaxine XR is just an expensive SSRI; most patients will require at least 150 mg a day (and often more) in order to benefit from both 5-HT and NE enhancement with venlafaxine. Venlafaxine XR also has a worrisome cardiovascular profile, which includes hypertension at higher doses. In a venlafaxine study submitted to the FDA to establish efficacy and safety, 2% of patients on placebo developed clinical hypertension. The incidence was 3% with venlafaxine XR at 75 mg daily. At 150 mg of venlafaxine daily, however, the incidence of clinical hypertension increased to about 5%, and at more than 225 mg daily, it reached 8% to 13%. All venlafaxine XR patients must have their blood pressure monitored because, depending on the dose, as many as 1 in 8 may develop clinical hypertension.35

A group at the University of Pittsburgh published data comparing remission rates using SSRIs and venlafaxine. Using data from 8 comparable randomized, double-blind studies of MDD, they examined response rates in 851 venlafaxine patients and 748 fluoxetine, paroxetine, or fluvoxamine patients, and compared the response rates with 446 placebo-treated patients. Of note, all studies were funded by the same pharmaceutical company, not all had been published, and the bias in patient selection was toward patients who had previously failed SSRIs. Forty-five percent of venlafaxine-treated patients reached remission, defined as ≤7 on the HAM-D17. For SSRIs, 35% of patients achieved remission, and for placebo patients, 25% reached remission. This study identified a relative benefit ratio of 40% for SSRIs compared with 80% for venlafaxine.36

Duloxetine is an experimental dual-action antidepressant for treatment of depression, with FDA approval expected in 2004. Duloxetine also has limitations. The incidence of nausea approaches 20% during the first week of therapy. Discontinuation syndrome has been reported with duloxetine, as it also has with venlafaxine.37

### Strategies to Achieve Remission

To ensure remission, several steps are necessary. First, clinicians must diagnose all symptoms appropriately. Then, choosing a treatment that can provide remission—that is, an antidepressant that works on multiple transmitters should be strongly considered—and employing it at adequate doses is the next step. Clinicians need to work with patients to help them adhere to treatment and educate them about the critical goal: remission. Finally, combination and augmentation strategies may be needed for treatment refractory of depressed patients after monotherapy fails.38

Studies examining combination strategies have reported mixed results overall. This may be due to the treatment refractory nature of some of these patients. Use of a single-acting agent (e.g., SSRI) may be less likely to lead to remission than combining it with an agent that acts on a different neurotransmitter system.
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(e.g., desipramine). Additionally, several studies confirm that combined treatment (combining medication with psychotherapy) produces better response in moderate to severe depression than either therapy alone.30-42

Conclusion

As we look for new and better antidepressants, optimizing efficacy, improving safety, and increasing tolerability in both the acute and long-term will be essential goals. For now, the focus on enhancing treatment success is crucial. Nearly half of all patients discontinue their antidepressant medication within the first or second month of therapy, often due to poor tolerability.43 Thus, choosing an antidepressant with the greatest likelihood of remission is important, as is achieving remission in a more rapid time frame. Selecting medications based on their side-effect profile may enhance adherence, although there is limited clinical trial data to support this hypothesis.

In mental health, clinicians are moving toward treatment algorithms as we accrue evidence about what works best. These algorithms address many possible clinical problems and include medication, therapy, and even electroconvulsive therapy for a very small percentage of the depressed population. As antidepressants have evolved, we have learned that multiple mechanisms may be the key to symptom remission. We know that improved outcomes occur because a better selection of antidepressants is available, evidence suggests appropriate dosing, and the importance of thorough and frequent monitoring is better appreciated.

DISCLOSURES

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REFERENCES


