CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will prescribe antidepressant drugs more confidently on the basis of the characteristics of the patient and the various drugs

ELIZABETH SHULTZ, DO
Department of Psychiatry and Psychology, Cleveland Clinic; Clinical Instructor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

DONALD A. MALONE, JR., MD
Chair, Department of Psychiatry and Psychology, Cleveland Clinic; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

A practical approach to prescribing antidepressants

ABSTRACT

Although antidepressant drugs do not differ much in their efficacy rates, the particular characteristics of one drug may make it a better choice in a given patient. This article provides insight into the art of prescribing antidepressants in primary care, with recommendations for prescribing for patients with chronic pain, sexual dysfunction, anxiety, chronic fatigue syndrome, fibromyalgia, severe insomnia, old age, diabetes, and heart problems.

KEY POINTS

We suggest that clinicians become familiar with one drug from each class of antidepressants.

Many antidepressants are also approved for conditions other than depression, and for patients who have both depression and one or more of these comcomitant conditions, these drugs can have a "two-for-one" benefit.

Adverse effects of an antidepressant are usually predictable on the basis of the drug's mechanism of action.

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With the variety of drugs available for treating depression, choosing one can be daunting. Different agents have characteristics that may make them a better choice for different types of patients, but even so, treating any kind of mental illness often requires an element of trial and error.

Primary care providers are on the frontline of treating mental illness, often evaluating patients before they are seen by a psychiatrist. The purpose of this article is to provide insight into the art of prescribing antidepressants in the primary care setting. We will discuss common patient presentations, including depressed patients without other medical comorbidities as well as those with common comorbidities, with our recommendations for first-line treatment.

We hope our recommendations will help you to navigate the uncertainty more confidently, resulting in more efficient and tailored treatment for your patients.

BASELINE TESTING

When starting a patient on antidepressant drug therapy, we recommend obtaining a set of baseline laboratory tests to rule out underlying medical conditions that may be contributing to the patient's depression or that may preclude the use of a given drug. (For example, elevation of liver enzymes may preclude the use of duloxetine.) Tests should include:

- A complete blood cell count
- A complete metabolic panel
- A thyroid-stimulating hormone level.

Electrocardiography may also be useful, as some antidepressants can prolong the QT interval or elevate the blood levels of other drugs with this effect.

Drugs discussed this article

Amitriptyline (Elavil)
Bupropion (Wellbutrin, Zyban)
Buspirone (Buspar)
Citalopram (Celexa)
Clomipramine (Anafranil)
Clonazepam (Klonopin)
Desvenlafaxine (Pristiq)
Doxepin (Sinequan)
Duloxetine (Cymbalta)
Escitalopram (Lexapro)
Fluoxetine (Prozac)
Imipramine (Tofranil)
Maprotiline (Deprilept, Ludiomil, Psymion)
Milnacipran (Savella)
Mirtazapine (Remiron)
Nefazodone (Serzone)
Nortriptyline (Aventyl, Pamelor, Norpress)
Paroxetine (Paxil)
Phenelzine (Nardil)
Selegiline (Eldepryl)
Sertraline (Zoloft)
Sildenafil (Viagra)
Tadalafil (Cialis)
Tranycypromine (Parnate)
Trazodone (Desyrel)
Venlafaxine (Effexor)

Start antidepressants at half the normal dose, and titrate upward as tolerated about every 14 days

GENERAL TREATMENT CONSIDERATIONS

There are several classes of antidepressants, and each class has a number of agents. Research has found little difference in efficacy among agents. So to simplify choosing which one to use, we recommend becoming comfortable with an agent from each class, ie:

- A selective serotonin reuptake inhibitor (SSRI)
- A selective serotonin-norepinephrine reuptake inhibitor (SNRI)
- A tricyclic antidepressant (TCA)
- A monoamine oxidase (MAO) inhibitor.

Each class includes generic agents, many of which are on the discount lists of retail pharmacies. **TABLE 1** shows representative drugs from each class, with their relative costs.

Start low and go slow. In general, when starting an antidepressant, consider starting at half the normal dose, titrating upward as tolerated about every 14 days. This approach can minimize side effects. For example, if prescribing fluoxetine, start with 10 mg and titrate every 2 weeks based on tolerance and patient response. That said, each patient may respond differently, requiring perhaps a lower starting dose or a longer titration schedule.

Anticipate side effects. Most of the side effects of an antidepressant drug can be explained by its mechanism of action. Although side effects should certainly be considered when choosing an agent, patients can be reassured that most are transient and benign. A detailed discussion of side effects of antidepressant drugs is beyond the scope of this article, but a review by Khawam et al[1] was published earlier in this journal.

Reassess. If after 4 to 6 weeks the patient has had little or no response, it is reasonable to switch agents. For a patient who was on an SSRI, the change can be to another SSRI or to an SNRI. However, if two SSRIs have already failed, then choose an SNRI. Agents are commonly cross-tapered during the switch to avoid abrupt cessation of one drug or the increased risk of adverse events such as cytochrome P450 interactions, serotonin syndrome, or hypertensive crisis (when switching to an MAO inhibitor).

Beware of interactions. All SSRIs and SNRIs are metabolized through the P450 system in the liver and therefore have the potential for drug-drug interactions. Care must be taken when giving these agents together with drugs whose metabolism can be altered by P450 inhibition. For TCAs, blood levels can be checked if there is concern about toxicity; however, dosing is not strictly based on this level. Great care should be taken if a TCA is given together with an SNRI or an SSRI, as the TCA blood level can become significantly elevated. This may result in QT interval prolongation, as mentioned earlier.

Refer. Referral to a psychiatrist is appropriate for patients for whom multiple classes have failed, for patients who have another psychiatric comorbidity (such as psychosis, hypomania, or mania), or for patients who may need hospitalization. Referral is also appropriate if the physician is concerned about suicide risk.

PATIENTS WITH MAJOR DEPRESSION ONLY

For a patient presenting with depression but no other significant medical comorbidity, the

first-line therapy is often an SSRI. Several generic SSRIs are available, and some are on the discount lists at retail pharmacies.

Symptoms should start to improve in about 2 weeks, and the optimal response should be achieved in 4 to 6 weeks of treatment. If this does not occur, consider either adding an augmenting agent or switching to a different antidepressant.

PATIENTS WITH CHRONIC PAIN

Chronic pain and depression often go hand in hand and can potentiate each other. When considering an antidepressant in a patient who has both conditions, the SNRIs and TCAs are typically preferred. Some SNRIs, namely duloxetine and milnacipran, are approved for certain chronic pain conditions, such as fibromyalgia. SNRIs are frequently used off-label for other chronic pain conditions such as headache and neuropathic pain.[2]

TCAs such as amitriptyline, nortriptyline, and doxepin are also often used in patients with chronic pain. These agents, like the SNRIs, inhibit the reuptake of serotonin and norepinephrine and are used off-label for neuropathic pain,[3,4] migraine, interstitial cystitis,[5] and other pain conditions.[6–9]

For TCAs and SNRIs, the effective dose range for chronic pain overlaps that for depression. However, TCAs are often given at lower doses to patients without depression. We recommend starting at a low dose and slowly titrating upward to an effective dose. SNRIs are often preferred over TCAs because they do not have anticholinergic side effects and because an overdose is much less likely to be lethal.

PATIENTS WITH SEXUAL DYSFUNCTION

One of the more commonly reported side effects of antidepressants is sexual dysfunction, generally in the form of delayed orgasm or decreased libido.[10] Typically, these complaints are attributed to SSRIs and SNRIs; however, TCAs and MAO inhibitors have also been associated wth sexual dysfunction.

Both erectile dysfunction and priapism have been linked to certain antidepressants. In particular, trazodone is a known cause of

TABLE 1
Representative antidepressants

Class and examples	Typical daily dose	Maximum dose	Cost[a]
Tricyclic antidepressants (TCAs)			
Amitriptyline	25–150 mg,[b,c]	300 mg	$
Imipramine	25–150 mg	300 mg	$$
Clomipramine	25–150 mg	300 mg	$$
Nortriptyline	25–150 mg	200 mg	$
Selective serotonin reuptake inhibitors (SSRIs)			
Fluoxetine	10–40 mg	80 mg	$
Paroxetine	20–40 mg	50 mg	$
Sertraline	50–200 mg	200 mg	$
Citalopram	10–40 mg	40 mg	$
Escitalopram	10–20 mg	30 mg	$$
Serotonin-norepinephrine reuptake inhibitors (SNRIs)			
Duloxetine	30–90 mg	120 mg	$$$
Desvenlafaxine	50–100 mg	100 mg	$$$
Nefazodone	200–600 mg[d]	600 mg	$$
Venlafaxine	37.5–225 mg	375 mg	$$
Trazodone	25–200 mg for sleep[b] 150 mg for depression[d]	600 mg	$
Dopamine-norepenphrine reuptake inhibitor			
Bupropion	100–300 mg	400–450 mg[e]	$–$$$
Alpha-2 agonist			
Mirtazapine	15–30 mg[b]	45 mg	$$
Monoamine oxidase (MAO) inhibitors			
Phenelzine	15–45 mg	60–90 mg	$$
Selegiline[f]	6 mg/24 h	12 mg/24 h	$$$
Tranylcypromine	10–30 mg	60 mg	$$

[a] $ = on discount list ($4 or less for 30-day supply), $$ = generic available or relatively low-cost brand name, $$$ = no generic available
[b] At bedtime
[c] Can be divided
[d] In divided doses
[e] Depending on formulation
[f] Selegiline transdermal system (Emsam patch)

priapism. Even if using low doses for sleep, male patients should be made aware of this adverse effect.

Switching from one agent to another in the same class is not likely to improve sexual side effects. In particular, all the SSRIs are similar in their likelihood of causing sexual dysfunction. In a patient taking an SSRI who experiences this side effect, switching to bupropion[11] or mirtazapine[12] can be quite useful. Bupropion acts primarily on dopamine and norepinephrine, whereas mirtazapine acts on serotonin and norepinephrine but in a different manner from SSRIs and SNRIs.

Adjunctive treatment such as a cholinergic agonist, yohimbine (contraindicated with MAO inhibitors), a serotonergic agent (eg, buspirone), or a drug that acts on nitric oxide (eg, sildenafil, tadalafil) may have some utility but is often ineffective. Dose reduction, if possible, can be of value.

PATIENTS WITH ANXIETY

Many antidepressants are also approved for anxiety disorders, and still more are used off-label for this purpose. Anxiety and depression often occur together, so being able to treat both conditions with one drug can be quite useful.[13] In general, the antidepressant effects are seen at lower doses of SSRIs and SNRIs, whereas more of the anxiolytic effects are seen at higher doses, particularly for obsessive-compulsive disorder.[14]

Depressive symptoms should start to improve about 2 weeks after treatment starts

First-line treatment would be an SSRI or SNRI. Most anxiety disorders respond to either class, but there are some more-specific recommendations. SSRIs are best studied in panic disorder, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Fluoxetine, citalopram, escitalopram, and sertraline[15] can all be effective in both major depressive disorder and generalized anxiety disorder. Panic disorder also tends to respond well to SSRIs. SNRIs have been evaluated primarily in generalized anxiety disorder but may also be useful in many of the other conditions.

Additionally, mirtazapine (used off-label)[12] and the TCAs[16–18] can help treat anxiety. Clomipramine is used to treat obsessive-compulsive disorder.[19] These drugs are especially useful for nighttime anxiety, as they can aid sleep. Of note, the anxiolytic effect of mirtazapine may be greater at higher doses.

MAO inhibitors often go unused because of the dietary and medication restrictions involved. However, very refractory cases of certain anxiety disorders may respond preferentially to these agents.

Bupropion tends to be more activating than other antidepressants, so is often avoided in anxious patients. However, some research suggests this is not always necessary.[20] If the anxiety is secondary to depression, it will often improve significantly with this agent.

When starting or increasing the dose of an antidepressant, patients may experience increased anxiety or feel "jittery." This feeling usually passes within the first week of treatment, and it is important to inform patients about this effect. "Start low and go slow" in patients with significant comorbid anxiety. Temporarily using a benzodiazepine such as clonazepam may make the transition more tolerable.

PATIENTS WITH CHRONIC FATIGUE SYNDROME OR FIBROMYALGIA

Increasing recognition of both chronic fatigue syndrome and fibromyalgia has led to more proactive treatment for these disorders. Depression can go hand in hand with these disorders, and certain antidepressants, namely the SNRIs, can be useful in this population.

More data exist for the treatment of fibromyalgia. Both duloxetine and milnacipran are approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia.[21] Venlafaxine is also used off-label for this purpose. SSRIs such as fluoxetine and citalopram have had mixed results.[21–23] TCAs have been used with some success; however, their side effects and lethal potential are often limiting.[21,24,25] A recent study in Spain also suggested there may be benefit from using MAO inhibitors for fibromyalgia, but data are quite limited.[26]

The data for treating chronic fatigue syndrome with SSRIs, SNRIs, or MAO inhibitors are conflicting.[27–29] However, managing the co-existing depression may provide some relief in and of itself.

PATIENTS WITH FREQUENT INSOMNIA

Insomnia can be a symptom of depression, but it can also be a side effect of certain antidepressants. The SSRIs and SNRIs can disrupt sleep patterns in some patients by shortening the rapid-eye-movement (REM) stage.[30,31]

In patients with severe insomnia, it may be best to first recommend taking the antidepressant in the morning if they notice worsening sleep after initiating treatment. Patients can be told with any antidepressant, "If it makes you tired, take it at night, and if it wakes you up, take it in the morning." Of note, a recent South African study suggested that escitalopram may be able to improve sleep.[32]

If that does not solve the problem, there are other options. For instance, mirtazapine, particularly in doses of 15 mg or 30 mg, aids depression and insomnia. At higher doses (45 mg), the sleep-aiding effect may be reduced. Low doses of TCAs, particularly doxepin, maprotiline (technically speaking, a tetracyclic antidepressant), amitriptyline, and nortriptyline can be effective sleep aids. These agents may be used as an adjunct to another antidepressant to enhance sleep and mood. However, the TCAs also shorten the REM stage of sleep.[33]

The previously mentioned drug interactions with SSRIs and SNRIs also need to be considered. Caution should be used when discontinuing these medications, as patients may experience rebound symptoms in the form of much more vivid dreams. MAO inhibitors may worsen insomnia because they suppress REM sleep.[34]

Trazodone is another agent that at lower doses (25–150 mg) can be an effective, nonaddicting sleep aid. When used as an antidepressant, it is generally prescribed at higher doses (300–400 mg), but its sedating effects can be quite limiting at these levels. It is important to remember the possibility of priapism in male patients.

GERIATRIC PATIENTS

Old age brings its own set of concerns when treating depression. Elderly patients are more susceptible to potential bradycardia caused by SSRIs. The TCAs have the more worrisome cardiac side effect of QTc prolongation. TCAs can slow cognitive function, whereas the SSRIs, bupropion, and the SNRIs tend not to affect cognition. Escitalopram and duloxetine have been suggested to be particularly effective in the elderly.[35,36] A study from the Netherlands linked SSRIs with increased risk of falling in geriatric patients with dementia.[37] Constipation, which could lead to ileus, is increased with TCAs and certain other agents (ie, paroxetine) in the geriatric population.

Mirtazapine is often very useful in elderly patients for many reasons: it treats both anxiety and depression, stimulates appetite and weight gain, can help with nausea, and is an effective sleep aid. Concerns about weight, appetite, and sleep are particularly common in the elderly, whereas younger patients can be less tolerant of drugs that make them gain weight and sleep more. Normal age-related changes to the sleep cycle contribute to decreased satisfaction with sleep as we age. In addition, depression often further impairs sleep. So, in the elderly, optimizing sleep is key. Research has also shown mirtazapine to be effective in patients with both Alzheimer dementia and depression.[38]

DIABETIC PATIENTS

Chronic pain and depression often go hand in hand and can potentiate each other

One of the more worrisome side effects of psychiatric medications in diabetic patients is weight gain. Certain antidepressants have a greater propensity for weight gain and should likely be avoided as first-line treatments in this population.[12] Typically, these agents include those that have more antihistamine action such as paroxetine and the TCAs. These agents also may lead to constipation, which could potentially worsen gastroparesis. Mirtazapine and the MAO inhibitors are also known to cause weight gain.

Bupropion and nefazodone are the most weight-neutral of all antidepressants. Nefazodone has fallen out of favor because of its potential to cause fulminant liver failure in rare cases. However, it remains a reasonable option for patients with comorbid anxiety and depression who have significant weight gain with other agents.

SSRIs and MAO inhibitors may improve or be neutral toward glucose metabolism, and some data suggest that SNRIs may impair this process.[39]

PATIENTS WITH CARDIAC CONDITIONS

Major depression often coexists with cardiac conditions. In particular, many patients develop depression after suffering a myocardial infarction, and increasingly they are being treated for it.[40] Treatment in this situation is appropriate, since depression, if untreated, can increase the risk of recurrence of myocardial infarction.[41]

However, there are many concerns that accompany treating depression in cardiac patients. Therefore, a baseline electrocardiogram should be obtained before starting an antidepressant.

TCAs and tetracyclic agents have a tendency to prolong the QTc interval and potentiate ventricular arrhythmias,[42] so it may be prudent to avoid these in patients at risk. These agents can also significantly increase the pulse rate. This tachycardia increases the risk of angina or myocardial infarction from the anticholinergic effects of these drugs.

In February 2013, the FDA issued a warning about possible arrhythmias with citalopram at doses greater than 40 mg in adult patients[43]; however, research has suggested citalopram is effective in treating depression in cardiac patients.[44] Research has not shown an increase in efficacy at doses greater than 40 mg daily, so we recommend following the black-box warning.

TCAs and MAO inhibitors can also cause orthostatic hypotension. On the other hand, consuming large amounts of tyramine, in foods such as aged cheese, can precipitate a hypertensive crisis in patients taking MAO inhibitors.

Which antidepressants tend to be safer in cardiac patients? Sertraline has been shown to be safe in congestive heart failure and coronary artery disease,[45–47] but the SSRIs are typically safe. Fluoxetine has shown efficacy in patients who have had a myocardial infarction.[48] Mirtazapine has also been shown to be efficacious in cardiac patients.[49] Nefazodone, mirtazapine, bupropion, SSRIs, and SNRIs have little or no tendency toward orthostatic hypotension.

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***ADDRESS**: Donald A. Malone, Jr., MD, Department of Psychiatry and Psychology, P57, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: maloned@ccf.org*