10 Atypical Antidepressants

Essential Concepts

- Trazodone is an excellent sleep aid but can cause medically important priapism.
- Bupropion is a generally well-tolerated agent, has a novel mechanism, and is especially useful in avoiding or treating sexual dysfunction.
- Mirtazapine also has a novel mechanism and a low rate of sexual dysfunction but is sedating and associated with weight gain.
- Venlafaxine may possess greater efficacy in treatment-refractory or melancholic depression but is associated with significant serotonergic withdrawal symptoms. It also has been shown to have a greater risk of cardiovascular problems, including sudden death, than previously acknowledged.
- Duloxetine is a purely noradrenergic agent marketed to have special benefits for depression-associated physical symptoms, although this purported benefit is not proven greater than with any other antidepressant.

TRAZODONE (DESYREL)

The first new medication developed after the tricyclic antidepressants (TCAs) was trazodone, which entered the market in the late 1980s. Trazodone was seen initially as being similar to TCAs but with the major benefit of not causing cardiac arrhythmias and therefore not being dangerous in overdose. Trazodone was dosed similarly to TCAs, requiring about 300 mg per day or more for effect, which often led to sedation. As a result, trazodone soon developed a niche as a sleep aid, especially in low doses (25 mg per day to 150 mg per day). This use has gained popularity, especially in polypharmacy with serotonin reuptake inhibitors (SRIs) because SRIs cause some disruption in sleep architecture, and trazodone normalizes this disrupted sleep architecture.

I suggest caution in viewing trazodone as an all-around safe anti-insomnia agent, however, because in my experience, it is used frequently for insomnia in patients with bipolar disorder. As will be discussed in more detail later, patients with bipolar disorder sometimes are sensitive to antidepressant medications, with potential worsening of mood episodes over time. Even low doses of trazodone, which theoretically do not possess full antidepressant effects, may contribute to mood destabilization in bipolar disorder. It is important to remember that insomnia is a very common symptom in bipolar disorder and in fact can reflect the prodromal onset of a manic episode; in that setting, the use of trazodone actually can worsen manic symptoms and thereby worsen insomnia. In nonbipolar depression, however, trazodone is a safe and effective sleep aid. Besides sedation, it is relatively well tolerated. One side effect of note is priapism, which, though rare (occurring in about 1 in 6,000 patients), can be medically risky if prolonged. This effect often occurs at low doses and in the first month of treatment. There is a theoretical risk of serotonin syndrome when combining even low-dose trazodone with SRIs, but this risk is quite rare and limited to isolated case reports.

It is important to note that trazodone has a unique mechanism of action that foreshadowed many later medications. It has serotonin reuptake effect and also blocks 5HT-2 receptors. By blocking 5HT-2 receptors, it reduces sexual dysfunction compared with the class of SRI medications.

Nefazodone shares this mechanism and is a chemical derivative of trazodone with similar dosing and side effects. It is also sedating, although somewhat less than trazodone. It does not have a significant risk of priapism. As noted earlier, it has reduced sexual dysfunction rates. Therefore, nefazodone tends to be used as an alternative to SRIs when patients improve but experience intolerable sexual dysfunction. As a medication with serotonin reuptake effects, nefazodone can cause gastrointestinal side effects characteristic of the SRI class (see Chapter 11). It also can cause orthostatic hypotension. Nefazodone is a strong inhibitor of the hepatic cytochrome P450 3A4 enzyme, and thus drug interactions can occur with agents metabolized by that system, which can include some antihistamine and antifungal agents. Recently, nefazodone was implicated in some cases of hepatic failure (1 case per 250,00 to 300,000 patient-years), which resulted in a black box warning and a marked decline in its use.

BUPROPION (WELLBUTRIN)

We understand best what bupropion *does not* do biochemically. It does not directly affect serotonergic receptors or mechanisms. It does not directly affect noradrenergic receptors. It possesses mild indirect stimulatory effects on noradrenergic neurons, and it is a very mild dopamine reuptake inhibitor. These mild effects on noradrenergic and dopaminergic function do not explain the antidepressant benefits of this agent, however. We can say, nonetheless, that this is an effective antidepressant that clearly has no serotonergic effects.

Bupropion did not achieve as much early popularity as the SRIs mainly owing to a few initial cases of seizures, which tended to occur in patients with concomitant bulimia nervosa. Hence bupropion has become contraindicated in patients with active eating disorders. The seizure risk loomed large in the minds of clinicians, however, because clinical trial data indicated a 0.4% risk with bupropion compared with a 0.1% risk with SRIs. The seizure risk increased even further with doses of bupropion above the 450 mg per day level. Seizures also were more likely if the medication was dosed at more than 150 mg per day. Since the minimum effective dose of this immediate-release formulation of bupropion was 300 mg per day, the drug needed to be dosed multiple times daily, which increased the risk of noncompliance. For these reasons, the standard formulation of immediate-release bupropion was not used as first-line treatment of unipolar depression.

Two slow-release formulations of bupropion (Wellbutrin SR and XL) have been developed that avoid most of these problems. The slow-release agents have a seizure risk of 0.1% below its highest dose of 400 mg per day. For the SR formulation, the minimal effective dose is 200 mg per day, and the largest amount that can be given in one dose is 200 mg per day. Hence those who respond to 200 mg per day will need only once-daily dosing. At most, in those who need up to 400 mg per day, the agent will require twice-daily dosing. With the XL formulation, 300 mg can be given in one dose. As a result, I generally recommend use of one of the slow-release formulations (Table 10.1).

Any formulation of bupropion can be stimulating and thereby interfere with sleep. Therefore, the last dose of bupropion generally should not be given after 5 P.M. In some patients, heightened anxiety or panic symptoms can occur. In my experience, this is more frequent in persons with previous diagnoses of primary panic disorder. However, in persons with generalized anxiety disorder or anxiety symptoms that occur only during

TABLE 10.1. Atypical Antidepressants

Drug	*Effective Dose (mg/day)*	*Mechanism of Action*	*Drug Interactions*	*Comments*
Trazodone (Desyrel)	300–400	Serotonin reuptake plus 5HT-2 receptor blockade	Potential (though rare) serotonin syndrome in combination with SRIs	No cardiac effects; sedating at higher doses; useful for insomnia
Bupropion (Wellbutrin SR, XL)	200–400	No serotonin effects; mild noradrenergic serotonergic, stimulation	Moderate inhibition of cytochrome P450 2D6 enzymes, thus potentially increasing SRI blood levels	Effective; limited side effects; no sexual dysfunction; can be stimulating
Duloxetine (Cymbalta)	20–60	Norepinephrine reuptake inhibitor	None	Reported benefit for physical symptoms

major depressive episodes, anxiety symptoms often seem linked to mood symptoms. By improving depression, bupropion can improve anxiety in these patients. As a consequence, I do not think that it is necessarily the case that bupropion should be avoided in patients with anxiety symptoms along with major depression. Again, if the anxiety seems linked to the depression, bupropion should help. If the patient has a long-standing primary panic disorder, bupropion would not likely be a first choice. Even if anxiety develops or worsens on bupropion, the drug can either be reduced in dose or changed, or anxiety can be treated with concomitant benzodiazepines. Clinicians need to take into account the entire range of patients' symptoms and side effects in making such decisions.

Bupropion does not cause sexual dysfunction and can, in fact, improve sexual function. It serves as a good alternative to SRIs in patients who experience or wish to avoid sexual dysfunction.

TIP

Many clinicians have taken to combining SRIs and bupropion either to treat sexual dysfunction or to augment the effect of one agent. This combination, by using different mechanisms of action, seems logical for treatment-refractory depression, but it was not especially effective in STAR-D.

Generally, bupropion has been considered to have minimal drug interactions. However, a recent study suggests that bupropion in fact may inhibit the cytochrome P450 2D6 enzyme system, resulting in elevated SRI blood levels. Since this combination has become popular, attention should be paid to this drug interaction, which could result in increased SRI-like side effects.

Other novel uses of bupropion are worth mentioning. Marketed as Zyban, bupropion has been shown to assist with the stopping of cigarette use. Bupropion also has been associated with mild to moderate weight loss in a double-blind study.

MIRTAZAPINE

Mirtazapine blocks alpha-2 receptors, which exert a negative-feedback influence on noradrenergic and serotonergic neurons. Blocking those receptors therefore leads to increased noradrenergic and serotonergic neurotransmission. In addition, mirtazapine blocks some serotonin receptors. Like nefazodone and trazodone, it blocks 5HT-2 receptors, resulting in less sexual dysfunction. Further, mirtazapine blocks 5HT-3 receptors, which are located in the gut and are responsible for the gastrointestinal side effects (i.e., nausea, diarrhea) of SRIs. Consequently, there are fewer gastrointestinal side effects with mirtazapine than with standard SRIs.

KEY POINT

Mirtazapine blocks 5HT-2 receptors, resulting in less sexual dysfunction, and it also blocks 5HT-3 receptors, avoiding gastrointestinal side effects that are common with SRIs.

This novel mechanism may mean that some patients will respond to mirtazapine who have not responded to nefazodone or SRIs. Further, like nefazodone, mirtazapine is a good alternative agent for persons who respond to SRIs but develop intolerable sexual dysfunction. Also, if intolerable gastrointestinal side effects limit the tolerability of SRIs, mirtazapine may be a viable alternative.

Unfortunately, mirtazapine is sedating, and this agent also frequently causes weight gain, which is often intolerable to many patients. Sometimes it is felt that these effects, paradoxically, may be more common at lower than at higher doses of mirtazapine, although my experience has not supported this observation sufficiently. Mirtazapine does not clearly inhibit any hepatic enzymes. Rare cases of agranulocytosis have been reported with mirtazapine, although a direct association with this medication has not been established.

VENLAFAXINE

Venlafaxine has been marketed as a serotonergic/noradrenergic agent. There is some accuracy to this description, although the reality is much more complex. The mechanistic effects of venlafaxine are dose-dependent. At lower doses (below 150 mg per day), basically venlafaxine only blocks serotonin reuptake. In this sense, low-dose venlafaxine is more or less another SRI. At higher doses (above 150 mg per day), venlafaxine blocks increasingly higher amounts of norepinephrine reuptake. However, the amount of norepinephrine reuptake blockade that occurs with venlafaxine is not extremely high in vitro; that is, venlafaxine blocks norepinephrine reuptake only somewhat more than fluoxetine (which is advertised as anything more than an SRI) and much less than desipramine (the most potent noradrenergic TCA).

Some clinicians view venlafaxine as equivalent to combining an SRI (serotonin reuptake) with a TCA (norepinephrine reuptake). While this view is accurate in principle, it is not correct in practice because the amount of norepinephrine reuptake one obtains is much greater with a TCA than with venlafaxine. In contrast to what the profession was led to believe at the publication of the first edition, the idea of venlafaxine as a safer alternative to TCAs does not hold up to close examination. Analyses of U.K. overdose deaths indicated higher rates with venlafaxine than with SRIs but lower than with TCAs. Caution was encouraged in using venlafaxine in people with past cardiac disease. The manufacturer questions the concern of U.K. authorities regarding cardiovascular toxicity, yet it is unclear if all the data have been made public regarding the absence of

such risk. Given the fact that relevant data on safety and efficacy are not always provided by the pharmaceutical industry, my own view is that clinicians should be cautious in such matters. Thus I think that the question of cardiovascular risks with venlafaxine should be taken more seriously than in the past. I would recommend caution with its use, although this does not mean that it should not be used, any more than TCAs should not be used; it simply needs to be used with more medical caution than in the past.

The usual effective dose of this agent for unipolar depression is 150 to 225 mg per day, which indicates that some level of noradrenergic activity is needed for antidepressant effect. Some persons will respond at lower doses, and venlafaxine is indicated by the Food and Drug Administration (FDA) for the treatment of generalized anxiety disorder at a dose of 75 mg per day (a pure serotonergic dose not different from the SRI class in effects).

TIP

Venlafaxine may be more effective than SRIs for severely depressed patients.

Venlafaxine has been proven effective, and in some studies more effective than SRIs, in hospitalized patients with depression and in melancholic subtype of unipolar depression, with both types of patients being severely ill. In open studies, venlafaxine has appeared effective in samples of treatment-refractory depressed patients. Some clinicians have a general sense that venlafaxine may possess some greater efficacy than other newer antidepressants, but they frequently tend to hold off on using venlafaxine unless necessary owing to side effects such as sedation.

Venlafaxine is also rather clearly associated with serotonin withdrawal syndrome, which consists of increased anxiety and a range of physical symptoms that are not dangerous but are quite disturbing to patients. This withdrawal syndrome is thought to be related to half-life, thus being perhaps greatest with venlafaxine and least with fluoxetine. Immediate-release venlafaxine, which possesses a half-life of only about 5 hours, has been supplemented recently by an extended-release formulation (Effexor XR), which allows once-daily dosing. However, the serotonin withdrawal still occurs even with the XR formulation, although likely somewhat less frequently than with the immediate-release

formulation. Since the literature on this topic is not definitive, I find it is very helpful to explain the possibility to patients by saying that they might experience symptoms simulating a panic attack or a flulike syndrome but that these symptoms are not medically dangerous. With this kind of reassurance, patients will not go to emergency rooms owing to their unexplained physical symptoms, and they usually can last through the week or so in which they occur. Owing to the withdrawal syndrome, venlafaxine should be tapered gradually. For example, in someone taking 300 mg per day whom I want to switch to another agent, I would reduce venlafaxine to 225 mg per day for 3 days, then 150 mg per day for 3 days, then 75 mg per day for 4 days, then 37.5 mg per day for 5 days, then 37.5 mg every other day for 4 days, and then stop. The last 75 mg per day of the medication tends to be the most difficult step in the taper. Rarely, the symptoms are too severe or last longer than 1 week, and in those cases, I sometimes add low-dose fluoxetine (10 mg per day) to cover the taper off venlafaxine, and then I later taper fluoxetine gradually (5 mg per day per week).

Venlafaxine does not tend to affect hepatic enzymes and thus does not cause significant drug interactions.

CLINICAL VIGNETTE

The patient is a 27-year-old woman who has taken venlafaxine 150 mg per day for 4 years, along with gabapentin 1,600 mg per day, for unipolar depression and generalized anxiety disorder. She has not responded well in the past year, and her clinician makes a decision that she needs a new antidepressant. Since she also previously failed all SRIs and a few TCAs, the clinician decides to use an MAOI. In order to prepare for the MAOI, he needs to taper the patient off venlafaxine and allow for over a month before beginning the MAOI owing to the risk of serotonin syndrome. He reduces venlafaxine to 75 mg per day for 1 week, then 37.5 mg per day for 1 week, then discontinuation. Two weeks later, the patient calls with marked nausea and a flulike feeling. The patient is quite scared and is afraid that she went off venlafaxine too fast. The clinician reassures her that her symptoms will improve. A few days later, she calls reporting panic attacks, marked anxiety, a lightening-bolt sensation throughout her body, and the fear that her depression is returning. Again, the clinician notes her symptoms but asks her to wait a few days because these symptoms all can occur with serotonin withdrawal. If her

symptoms persist another week, he indicates that he will either resume venlafaxine or begin another seronotergic agent to help with the withdrawal. Within a week, the symptoms begin to improve, and they resolve completely in 2 weeks.

DULOXETINE

This new antidepressant is a pure norepinephrine reuptake inhibitor. As such, it is a modern version of desipramine. Its manufacturer included physical symptom assessment in its clinical trials, leading to permission from the FDA to market this agent for the treatment of depression, along with the physical symptoms associated with depression. This has led to the clinical conception that this agent may be especially useful for patients with depression and associated physical symptoms. Of course, most patients with depression also have associated physical symptoms. What is scientifically relevant is that one would need studies directly comparing duloxetine with other antidepressants for physical symptoms before one could say that duloxetine is preferentially more effective than other antidepressants for depression-related physical symptoms. We await such data. This is simply a noradrenergic antidepressant; as such, it may have utility as an alternative to SRIs or bupropion in patients who do not respond to those other agents or who have serotenergic-associated side effects. This role is no different from the potential benefits of desipramine, with the difference that duloxetine appears not to be associated with any risk of cardiac arrhythmia.

Serotonin Reuptake Inhibitors

Essential Concepts

- Serotonin reuptake inhibitors (SRIs) are not more effective than other antidepressants; their main advantage is tolerability.
- Fluoxetine has the longest half-life and the most noradrenergic effects.
- Sertraline has mild to moderate dopaminergic effects.
- Paroxetine has mild to moderate anticholinergic effects and, in higher doses, mild to moderate noradrenergic effects.
- Fluvoxamine is most used in obsessive-compulsive disorder.
- Citalopram is the most purely serotinergic of the SRIs and is especially well tolerated in the elderly.
- Sertraline and citalopram have the fewest drug interactions, fluoxetine the most, and paroxetine and fluvoxamine an intermediate amount.
- SRIs have a small but real risk of increased suicidality, especially related to causing mixed states in misdiagnosed bipolar depression or to causing akathisia.

EFFICACY AND SAFETY

SRIs have not been proven to be more effective than the tricyclic antidepressants (TCAs); rather, their advantage seems to be improved tolerability and patient acceptability. This is a strong point worth emphasizing. Many clinicians in the United States use SRIs almost exclusively, often going through all medications in this class, occasionally trying some of the newer atypical antidepressants, and rarely if ever using TCAs or monoamine oxidase inhibitors (MAOIs). This approach assumes that SRIs have equal or better efficacy than the other agents. In fact, TCAs, MAOIs, and venlafaxine are more effective than SRIs in specific populations, especially hospitalized and melancholic patients. Safety is an important