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New antidepressants: more options for tailoring treatment

KEY POINTS:

The newer antidepressant drugs are not more effective than older ones, but they cause fewer and less-severe side effects and thus are better accepted by patients.

The newer antidepressant drugs have a number of drug interactions. In particular, nefazodone should not be given with terfenadine, astemizole, or cisapride because of the danger of ventricular arrhythmias.

Depressed patients with anxiety or agitation may be more likely to benefit from an initial trial of a more sedating antidepressant such as nefazodone or paroxetine.

Patients with depressive symptoms such as lethargy and amotivation may do better with a more activating antidepressant such as fluoxetine, bupropion, or venlafaxine.

ABSTRACT: Newer antidepressant drugs cause fewer, less-severe side effects and therefore usually elicit better patient compliance than do older drugs. The newer drugs have slightly differing mechanisms of action and effects and thus offer additional options for tailoring treatment to the individual patient. Yet they are not completely innocuous and can cause serious drug interactions.

The introduction of fluoxetine in 1987 marked the beginning of an influx of new drugs that have transformed the medical management of depression (**TABLE 1**). Although treatment of depressive disorders is still challenging, as it has always been, the newer classes of drugs have specific advantages. This article reviews the therapeutic considerations posed by the expanding array of effective psychopharmacological agents.

DEPRESSION IN PERSPECTIVE

Depression is common, affecting 5.8% to 19% of people at some point in their lives.[1] According to 1990 statistics, depression cost the United States $12 billion in direct care and more than $31 billion in indirect costs.[2] Despite the continuing toll reflected by these data, depression is eminently treatable, with response rates that are not unfavorable in comparison to many common medical illnesses.

A range of symptoms

Major depressive disorder is a syndrome characterized by a persistently depressed and sometimes irritable mood lasting longer than 2 weeks. It is associated with several neurovegetative symptoms, including anorexia, insomnia, lack of energy, fatigue, lack of interest (anhedonia), impaired concentration, and guilt. Crying spells, hopelessness, and helplessness are also common. Suicidal ideation is especially troubling to patients, families, and clinicians. Psychomotor retardation or agita-

tion may occur. Significant impairment in occupational, physical, or interpersonal function is necessary to diagnose a major depressive episode.

Blocking serotonin reuptake

Antidepressant medications have been used extensively for about 40 years. Although their exact mechanism of action has not been established, they are thought to work by increasing synaptic transmission of various neurotransmitters. Initially, a disorder of norepinephrine was presumed responsible for depression, but attention has shifted to serotonin. Increased understanding of serotonin has resulted in the proliferation of serotonergic medications, commonly called selective serotonin-reuptake inhibitors (SSRIs).

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

Four SSRIs are currently available: fluoxetine, sertraline, paroxetine, and fluvoxamine (**TABLE 1**). These medications are useful for an array of mental illnesses: major depression, anxiety, panic disorders,[3] obsessive-compulsive disorder,[4] personality disorders,[5] eating disorders,[6] chronic pain and headache,[7] and premenstrual dysphoric disorder (formerly premenstrual syndrome).[8] The Food and Drug Administration lists fluoxetine, sertraline, and paroxetine as indicated for treating depression, fluvoxamine and fluoxetine for treating obsessive-compulsive disorder, and fluoxetine for treating bulimia.

These four drugs do not appear to differ clinically in efficacy, onset of action, or side effects.

Advantages of selective serotonin-reuptake inhibitors

The SSRIs (and other newer antidepressants) are no more or less effective than the older monoamine oxidase inhibitors and tricyclic antidepressants ("tricyclic" refers to their chemical structure, containing three carbon rings), but they have several advantages.

Better tolerated. Because they do not significantly affect central neurotransmitters other than serotonin, SSRIs cause significant-

TABLE 1

NEW ANTIDEPRESSANT DOSING INFORMATION

Drug	Dosage range (mg/day)	Usual dose (mg/day)	Geriatric dose (mg/day)*	Tablet strengths (mg)	Half-life (hours)	Dosing schedule
Selective serotonin-reuptake inhibitors						
Fluoxetine (Prozac)	10–80	20	10–20	10, 20†	84	Daily
Sertraline (Zoloft)	50–200	100	50	50, 100	26	Daily
Paroxetine (Paxil)	20–50	20	10–20	20, 30	21	Daily
Fluvoxamine (Luvox)	50–300	100	50–100	50, 100	15	Daily or twice daily
Other, related agents						
Venlafaxine (Effexor)	75–375	150–225	75–150	25, 37.5, 50, 75, 100	4–10	Twice or three times daily
Bupropion (Wellbutrin)	150–450	300	150–300	75, 100	8–24	Twice or three times daily
Nefazodone (Serzone)	300–600	400–500	300–500	100, 150, 200, 250	4–8	Twice a day

*Geriatric dose should not be determined by age alone. Patients of advanced age, ie, > 65 years, who also have concomitant medical illness of significant degree, should be considered candidates for lower starting doses.

†Also available as liquid 20 mg/5 cc

TABLE 2

ANTIDEPRESSANT DRUG INTERACTIONS

Antidepressant	Liver isoenzyme inhibited	Drug actions increased	Drug actions may be increased
Fluvoxamine	1A2	Caffeine Theophylline Tricyclic antidepressants Haloperidol	Phenacetin
Fluvoxamine Fluoxetine Sertraline	2C9	Diazepam Phenytoin Tolbutamide	Tricyclic antidepressants Warfarin
Fluoxetine Sertraline	2C19		Diazepam Tricyclic antidepressants Omeprazole Propranolol
Paroxetine Fluoxetine Sertraline Fluvoxamine	2D6	Tricyclic antidepressants Antiarrhythmics (type 1C) Haloperidol Clozapine Selective serotonin-reuptake inhibitors	Antipsychotics Antiarrhythmics Opiates Beta blockers Vinblastine Dextromethorphan
Nefazodone Sertraline Fluoxetine Fluvoxamine	3A4	Astemizole Terfenadine Cisapride Midazolam Alprazolam Carbamazepine	Benzodiazepines Calcium channel blockers

ly fewer anticholinergic, antihistaminic, and antiadrenergic side effects. Consequently, they are better tolerated, and patients comply with taking them better.

Easier to titrate. Because the starting dosage for newer agents is frequently effective, one need not escalate the dosage over several weeks as with most older agents.

Safer. Overdoses of tricyclic antidepressants can be fatal, whereas SSRIs are unlikely to cause significant morbidity or mortality if overdosage occurs.

Side effects of SSRIs

Characteristic adverse effects of SSRIs include gastrointestinal disturbances (nausea, vomiting, diarrhea), central nervous system effects (headache, insomnia, agitation), sexual dysfunction, and tremor.[9]

In most cases these side effects are self-limiting and transient, occurring during the first 1 to 2 weeks of therapy and then subsiding. Treatment includes decreasing the antidepressant dosage if therapeutically possible. Starting at a low dose and increasing it slowly can prevent these effects for most patients.

Gastrointestinal disturbances. In our experience, constipation is more frequent with paroxetine than with other SSRIs, and loose stools are more frequent with sertraline. Antidiarrheals and antiemetics can be tried for severe cases during the early part of treatment.

Central nervous system effects. Fluoxetine seems to cause more activation (ie, central nervous system stimulation, which individual patients may experience as anxiety or agitation) than do the other SSRIs.

Insomnia often can be relieved by adding a low dose of a sedating antidepressant such as trazodone 50 to 100 mg at bedtime. If a patient takes his or her SSRI at bedtime, taking it in the morning instead may relieve the sleep problem.

Sexual dysfunction typically involves delayed orgasm and decreased libido in both men and women. The problem sometimes persists after the SSRI is reduced in dosage or stopped, but it may resolve if the dosage is reduced and, in some cases, if the antihistamine cyproheptadine is added. This agent has serotonin antagonist activity; the dosage is 4 to 16 mg 1 or 2 hours before anticipated sexual activity.[10]

Other effects. Since SSRIs primarily act on serotonergic receptors, they have essentially no cardiotoxic effects, unlike tricyclic antidepressants, which can have a quinidine-like effect. A few, rare cases of bradycardia have been reported with fluoxetine. Paroxetine has weak anticholinergic properties and can sometimes cause bothersome dry mouth, constipation, and dizziness.

Pharmacokinetics of SSRIs

The SSRIs differ in their pharmacokinetic and pharmacodynamic profiles. For example, paroxetine, sertraline, and fluvoxamine have half-lives of approximately 24 hours and

achieve a steady state within the first week of treatment. They also lack clinically significant metabolites.

In contrast, fluoxetine may take more than 3 weeks to achieve a steady state, owing to prolonged elimination of its primary and active metabolite, norfluoxetine. This is a potential disadvantage of fluoxetine because it takes longer to clear; however, an advantage may be that patients can miss doses occasionally without deleterious effects.

Drug interactions with SSRIs

A major concern with SSRIs is their drug interactions, as they inhibit the hepatic cytochrome systems responsible for metabolizing many other agents. There are 34 cytochrome P450 isoenzymes, and antidepressants can inhibit five of them (1A2, 2C9, 2C19, 2D6, and 3A4), potentiating or prolonging the action of the drugs these enzymes inhibit (**TABLE 2**). Drug interactions are particularly important in medically ill patients, who frequently take several other essential medications.[11]

Inhibition of the P450-2D6 isoenzyme system can increase levels of:

- Tricyclic antidepressants
- Antipsychotics
- Beta blockers
- Antiarrhythmics
- Opiates
- Vinblastine
- Dextromethorphan

A small percentage of persons genetically lack this enzyme because of genetic polymorphism, making them even more susceptible to drug interactions. In these "poor metabolizers," any additional reduction of enzyme action by inhibitory drugs such as antidepressants can significantly increase the concentration of the poorly metabolized drug to toxic levels.

Of the SSRIs, paroxetine is the most potent inhibitor of this enzyme, and fluvoxamine the weakest.

Inhibition of other cytochrome systems can increase the action of:

- Warfarin
- Nonsteroidal anti-inflammatory drugs
- Phenytoin
- Calcium-channel blockers
- Ketoconazole
- Terfenadine

Prolonged prothrombin time. Patients receiving anticoagulant therapy should have their prothrombin times checked more frequently if they take an SSRI, especially early on in SSRI treatment, as the interaction can prolong the prothrombin time. Lower doses of warfarin may be necessary. Fluoxetine has been reported to increase bleeding times through decreased granular storage of serotonin in platelets. For this reason, some clinicians recommend checking bleeding times before surgery in patients taking SSRIs.[12]

Dosage and administration of SSRIs

Starting dosage. In most cases, the usual starting dosage is therapeutic and does not need to be increased. Some patients with significant anxiety may do better with lower initial dosages, ie, fluoxetine 10 mg/day, as these lower dosages may be less likely to produce side effects and exacerbate their anxiety. In these anxious patients, the dosage can slowly be increased to the usual dosage. In a few cases, dosages greater than the usual starting dosage may be required.

The effective starting dosage for fluoxetine is 20 mg/day, for sertraline 50 mg/day, and for paroxetine 20 mg/day. Fluvoxamine can be started at 50 mg at bedtime and increased safely in the first week to 50 mg twice a day.

Dosage schedule. Most recommendations favor giving fluoxetine, sertraline, and paroxetine once a day, in the morning, with food, to minimize gastrointestinal side effects. Twice-a-day dosage can be helpful for patients with prolonged gastrointestinal side effects.

Titration should be conservative. Liver disease slows SSRI metabolism and generally warrants lower dosages. Renal impairment slows metabolism less than liver disease, but in severe cases of renal impairment lower dosages are probably indicated. Elderly patients also may need lower dosages, as they may be more susceptible to side effects, including tremor, anxiety, restlessness, and insomnia.

Because the starting dosage for newer agents is frequently effective, one need not escalate the dosage over several weeks as with most older agents.

How long to treat?

As with all antidepressants, depressed mood does not improve immediately with SSRI therapy, sometimes taking take 3 to 6 weeks or longer to improve. Neurovegetative symptoms such as disturbances of sleep, appetite, and energy may respond sooner. After 6 to 8 weeks, a partial response may signal the need to increase the dosage; lack of response may indicate the need to change to another class of antidepressant.

If successful, antidepressant therapy should continue for at least 6 months. Patients

with severe or recurrent depression should probably keep taking medication longer, in some cases for life.

VENLAFAXINE

Venlafaxine strongly inhibits reuptake of both serotonin and norepinephrine. Early data suggest it has a more rapid onset of action than other antidepressants, and greater efficacy in cases resistant to other drugs. However, these findings are preliminary.[13]

Side effects of venlafaxine

Venlafaxine's side effects are similar to those of SSRIs and include nausea, nervousness, sweating, dizziness, and dry mouth. Sexual dysfunction has been reported but may be less common.

Nausea can be quite troublesome; therefore, low initial doses are encouraged.

Hypertension is a potentially serious side effect. Lower dosages can minimize this effect, since diastolic blood pressure increases by more than 10 mm Hg in only about 5% of patients taking less than 200 mg/day, but 13% of those taking more than 300 mg/day.

A major concern with SSRIs is their drug interactions, as they inhibit the hepatic cytochrome systems responsible for metabolizing many other agents.

Dosage and administration of venlafaxine

Venlafaxine has a much shorter half-life than SSRIs (4–10 hours), necessitating two or three doses per day. The recommended dosage is 75 to 375 mg/day in divided doses. A starting dosage of 25 to 37.5 mg once or twice a day is reasonable.

Although metabolized by the liver, venlafaxine does not greatly inhibit the cytochrome P450-2D6 enzyme system. Its use in patients with liver or kidney disease should be guided by caution, with lower starting dosages and conservative titration.

BUPROPION

Bupropion, a monocyclic (one carbon ring) antidepressant, was introduced in 1989. Its mechanism of action is poorly understood, but it is thought to act primarily by blocking reuptake of dopamine and, to a lesser extent, norepinephrine.[14] Considered an "atypical" antidepressant, it generates a different spectrum of neurochemical effects than do other antidepressants. This distinctive mechanism of action makes it particularly useful for patients who do not respond to other antidepressant medications.

Structurally similar to some amphetamines, bupropion can be useful as a stimulating antidepressant in atypical and melancholic depressions. (Amphetamines such as methylphenidate have been used for treating depression with particularly anergic features, ie, after a stroke.) A recent study of bupropion for treating attention-deficit disorder in children and adults was promising.[15]

Side effects of bupropion

Bupropion's side-effect profile is similar to that of SSRIs; however, it does not appear to cause sexual dysfunction. It has no significant cardiotoxic effects, so it is useful in medically ill and cardiac patients. Hypertension is an unlikely adverse effect but is more likely to occur in patients with preexisting hypertension than in those without it.

Seizures have been reported with bupropion therapy.[16] However, the incidence of seizures during bupropion therapy is comparable to that of other antidepressants if patients with risk factors for seizures are excluded. Therefore, patients with epilepsy, alcoholism, benzodiazepine dependence, eating disorders, or history of head trauma should receive other antidepressants.

Dosage and administration of bupropion

Bupropion's elimination half-life ranges from 8 to 24 hours; therefore, it is usually given twice or three times a day. The starting dosage is 75 or 100 mg twice a day and can be safely increased to 75 or 100 mg three times a day; the recommended dosage is 300 mg/day. The therapeutic dosage range is 150 to 450 mg/day in divided doses.

Doses must be limited to 150 mg and separated by at least 4 hours. More than 450 mg/day should be avoided to minimize seizure risk.

NEFAZODONE

Introduced in the United States in 1995, nefazodone is clinically effective and well tolerated. It has a unique pharmacologic profile: like SSRIs, it inhibits presynaptic reuptake of serotonin, but it also antagonizes postsynaptic serotonin receptors and weakly inhibits presynaptic norepinephrine reuptake.[17]

Side effects of nefazodone

The most common adverse effects of nefazodone are dry mouth, somnolence, dizziness, and nausea.[18] Although structurally similar to the older antidepressant trazodone, nefazodone causes minimal orthostatic changes and less sedation. No cases of priapism (a notorious side effect of trazodone) have been reported with nefazodone therapy. Sexual dysfunction appears much less common with nefazodone than with SSRIs.

Drug interactions with nefazodone

Several unique drug interactions can occur with nefazodone.

Alprazolam and triazolam levels can increase in patients taking nefazodone.

Terfenadine or astemizole should not be given with nefazodone, because nefazodone, like ketoconazole, inhibits cytochrome P450-354, which metabolizes these drugs. The resulting increased concentrations of these antihistamines can lead to potentially fatal ventricular arrhythmias of the torsade de pointes type.[19]

Cisapride is also metabolized by P450-3A4, and, given with nefazodone can also cause tachycardia and torsade de points.[20] Venlafaxine and tricyclic antidepressants are much less likely to inhibit P450-3A4 and are better options for patients who need to take one of these antihistamines or cisapride.[19]

Midazolam, often used intravenously for sedation in procedures such as colonoscopy, is also metabolized via the 3A4 pathway. Therefore, its coadministration in patients taking nefazodone may lead to increased sedation and respiratory depression, especially in the elderly.

Dosage and administration of nefazodone

Nefazodone has a relatively short elimination half-life, suggesting it should be given in frequent doses; however, twice-a-day dosing seems to be adequate. The recommended starting dosage is 100 mg twice a day, with an effective therapeutic dosage being 300 to 600 mg per day. Weekly adjustments in dosage may be needed during the initial weeks of therapy.

TOWARD A RATIONAL, TAILORED APPROACH

Newer agents such as SSRIs, venlafaxine, bupropion, and nefazodone are excellent options that are usually tried before traditional antidepressants such as tricyclics because of proven efficacy and fewer and less bothersome side effects. Because of the distinctive pharmacologic differences among these drugs, clinicians can better tailor antidepressant regimens for individual patients and their particular symptoms.

For example, depressed patients with anxiety or agitation may be more likely to benefit from an initial trial of a more sedating antidepressant such as nefazodone or paroxetine. On the other hand, patients with depressive symptoms such as lethargy and amotivation may do better with a more activating antidepressant such as fluoxetine, bupropion, or venlafaxine.

Nevertheless, older medications such as tricyclic antidepressants continue to be useful. Tricyclics such as amitriptyline and nortriptyline can alleviate not only depression but also insomnia and pain. However, the low dosages commonly used for insomnia (ie, amitriptyline 25 mg at bedtime) may not be high enough for treating depression—and higher doses increase the incidence of side effects. ■

As with all antidepressants, depressed mood does not improve immediately with SSRI therapy, sometimes taking 3 to 6 weeks or longer to improve.

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