

Antidepressant Choices in Primary Care: Which to Use First?

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INTRODUCTION

The past 15 years have seen a tremendous growth in the number of new medications to treat a variety of psychiatric disorders. In 1998 fluoxetine (Prozac) was marketed in the United States and ushered in a new era of medication treatments for major depression and anxiety disorders. As of 2000, fluoxetine had reached \$2 billion in United States sales¹ and no drug marketed has received as much attention and study. Several other selective serotonin reuptake inhibitors (SSRIs) were marketed soon after and their ease of use, favorable side effect profile, and safety in overdose has made them the first-line pharmacotherapy for mood and anxiety disorders. Along with the SSRIs, other antidepressants with different mechanisms of action have also been marketed and several others are in the final stages of clinical trials. Antidepressants accounted for a staggering global market of \$14.5 billion in 2003 and were the third-largest category of prescription medications behind antiulcerants and cholesterol-reducing agents.²

Numerous choices, however, can lead to confusion over which is the best first-line medication to prescribe for a patient with a mood or anxiety disorder. Despite advances in the treatment of depression and numerous medication options, it is estimated that over 50% of patients with major depressive disorder are not prescribed an adequate dose of antidepressants or are treated not long enough to remission.³ Spiraling prescription drug costs and increased growth in managed care are restricting drug choices and influencing prescribing practices. The recent FDA warnings reporting the possibility of increased agitation and suicidal behavior in patients prescribed the newer antidepressants also confounds the choice of which drug to use and when. This article reviews the characteristics of the various SSRIs and other newer antidepressants and discusses indica-

tions and potential reasons for selecting one over another.

SELECTING ANTIDEPRESSANTS

Are all of the antidepressants equally efficacious? This is unlikely given that not all people respond to the same antidepressant trial. Table 1 summarizes the newer antidepressants marketed in the United States and lists their FDA-approved indications and usual dosing ranges. The SSRIs are not interchangeable; some people tolerate and respond better to different medications in the same class. Only 50%-60%, however, will respond to any one drug trial, and treatment of depression and anxiety disorders often requires several medication trials until one is found to be effective and tolerable. However, there is no clear data that one drug is superior to another. Choosing a medication is based on side effect profile, patient factors, and symptom subtype. For example, a patient with poor energy and increased sleep might do well on bupropion. However, an anxious patient might find it too overstimulating. Strategic use of certain side effects can also be useful. Weight gain is more common with mirtazapine, paroxetine, and older tricyclic antidepressants. Many patients will not tolerate any weight gain, but some patients who have poor appetites or are very underweight might do well with a medication that increases appetite.

Patient age is also an important factor. Elderly patients are more likely to be more sensitive to side effects and take more medications, increasing the possibility of drug interactions. Avoidance of antidepressants that significantly induce or inhibit P450 isoenzymes is wise in this population.⁴ Gender is another factor as new data suggests that men may respond better to tricyclic antidepressants and less well to SSRIs than women.⁵ Comorbid medical illnesses also play a role in antidepressant selection. Tricyclic antidepressants may not exacerbate migraine headaches in sufferers as much as a SSRI. Cardiac patients are more sensitive to the QT-prolonging effects of tricyclics and this is generally not the best choice for them. Another important factor is patient/family history and patient preferences. What a patient or a genetically-

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Table 1. Newer Generation Antidepressants

Generic	Brand	FDA Indications	Usual Dose Range (in mg)
SSRIs			
Citalopram	Celexa	MDD	20-60
Escitalopram	Lexapro	MDD	10-20
Fluoxetine	Prozac generic	MDD, Panic OCD, PMDD Bulimia	20-60
Fluvoxamine	Luvox generic	OCD	100-200
Paroxetine	Paxil Paxil CR Perexa generic	MDD, Panic OCD, PTSD GAD, SAD	20-60
Sertraline	Zoloft	MDD, Panic OCD, SAD PTSD, PMDD	50-200
SNRI			
Venlafaxine	Effexor Effexor XR	MDD, GAD, SAD	150-300
5-HT2 Antagonists			
Nefazodone	Serzone generic	MDD	300-600
Others			
Bupropion	Wellbutrin Wellbutrin SR cessation Wellbutrin XL Zyban generic	MDD, smoking	200-450
Mirtazapine	Remeron Sol-tabs generic	MDD	15-45

Note: MDD=major depression, GAD=generalized anxiety disorder, SAD=social anxiety disorder, PD=panic disorder, PTSD=post traumatic stress disorder, OCD=obsessive compulsive disorder, PMDD=premenstrual dysphoric disorder.

Table 2. Comparisons of Costs of Antidepressants*

Drug	Quantity	Cost
fluoxetine 20 mg	30	\$33.99
Paxil CR 25 mg	30	\$87.99
Paroxetine 20mg	30	\$69.99
Zoloft 50mg	30	\$80.99
Celexa 20mg	30	\$77.99
Lexapro 10mg	30	\$76.99
Effexor XR 150mg	30	\$115.99
Wellbutrin XL 300mg	30	\$122.49
bupropion SR 150mg	60	\$95.99
bupropion 75mg	100	\$56.99
mirtazapine 30mg	30	\$77.99
nefazodone 150mg	60	\$38.99
nortriptyline 50mg	60	\$17.99

*Data taken from Walgreens.com on 10/1/04 and reflects costs to the consumer without insurance deductions.

related family member has responded to in the past predicts what they will respond to in the future. Patients are often clear about what side effects they are willing to tolerate. Finally, medication cost is important. Patients without prescription drug coverage or with high medication co-pays may be more compliant with an antidepressant that is available in a cheaper, generic form. Table 2 compares costs for an average monthly dose of the most commonly prescribed antidepressants. The next section will describe the individual antidepressants and discuss the pros and cons of selecting one over another.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

SSRIs selectively block the reuptake of 5-HT autoreceptors leading to increased serotonin in the neuronal synaptic clefts. This ultimately leads to down regulation of the receptors, which is considered to be the therapeutic effect. Although SSRIs are much more selective for 5-HT than the older tricyclics and MAOIs, they do vary in their degree of selectivity. The newest SSRIs—citalopram and escitalopram—are the most selective, while the older paroxetine, sertraline, and fluoxetine are much less selective.⁶ Paroxetine, with more anticholinergic blockade, is generally more sedating than citalopram, but also may alleviate acute anxiety better. All SSRIs are approved for the treatment of major depression and dysthymia. As Table 1 demonstrates, certain SSRIs have received FDA indications for a variety of anxiety disorders. However, SSRIs are used clinically to treat the anxiety disorders.

All SSRIs are metabolized through the C-P450 isoenzyme pathways. Table 3 summarizes the SSRIs and their C-P450 metabolic pathways. Fluoxetine has the most interactions on the P450 system and patients who are taking multiple medications are more at risk for potential drug interactions with fluoxetine than citalopram and escitalopram. Sertraline and fluoxetine have active metabolites leading to longer half-lives. Sertraline has a half-life of 48-72 hours; fluoxetine's is up to 1 week. Paroxetine, on the other hand, has an extremely short half-life of 15-20 hours, leading to a higher rate of discontinuation symptoms. Fluoxetine can be a good choice for a patient who frequently misses medication doses, but again, might be problematic for patients with comorbid medical conditions and on multiple medications.

Although SSRI side effects have been generally better tolerated than older tricyclics and MAOIs, they still have the potential to create uncomfortable symptoms. Gastrointestinal side effects are quite common and include nausea, diarrhea, abdominal cramping (worse with sertraline and venlafaxine), anorexia (worse with fluoxe-

tine), and constipation (worse with paroxetine and venlafaxine). Taking the medications with food, starting at one-half of the lowest target dose, and increasing dosages slowly helps to minimize this. Mirtazapine, an atypical antidepressant, generally does not cause these side effects, but may increase appetite and cause weight gain.

The SSRIs mentioned above are helpful in treating anxiety disorders. However, they may cause CNS activation, especially if started at high doses. These include insomnia, anxiety, and agitation (worse with fluoxetine). Paroxetine, due to its anticholinergic effects, generally is more likely to cause sedation. Taking SSRIs (except paroxetine) in the morning, starting at one-half of the lowest therapeutic dose and increasing it gradually minimizes this. Concurrent use of a benzodiazepine for anxiety or trazodone or mirtazapine for insomnia may also be useful.

Most side effects are transient, but potentially most distressing to patients are the sexual side effects, which are generally persistent. Up to 30%-40% of patients will experience decreased libido and/or inorgasmia.⁷ These side effects are a major source of early medication discontinuation and non-compliance. Unfortunately there are no clear solutions, and most treatment suggestions are merely anecdotal. Often, the best solution is switching to a medication less likely to produce sexual side effects (bupropion, nefazodone, and mirtazapine).^{8,9}

Other common side effects include dry mouth, headaches (including migraine exacerbation), weight gain (low with most SSRIs, but more common with paroxetine), tremor, and akathisia. Fortunately, these drugs are relatively safe in overdose.¹⁰ When these drugs are discontinued, it is wise to taper them slowly over a period of weeks to avoid discontinuation symptoms. These include flu-like symptoms of malaise, nausea, headaches, insomnia, agitation, and paresthesias. They are worse with paroxetine and venlafaxine due to their short half-lives, and rare with fluoxetine.¹¹ A good general guide is to cut the medication in half each 1-2 weeks until discontinued. Patients who have particular difficulty may be switched directly to fluoxetine and then tapered off.

OTHER ANTIDEPRESSANTS

Nefazodone (Serzone) is a 5-HT₂ antagonist and also has mild serotonin reuptake and mild stimulation at the 5-HT_{1A} receptor. It is similar to trazodone, an older antidepressant used mostly now as a hypnotic due to its significant sedating effects. However, it is less likely than trazodone to cause sedation and dizziness. Nefazodone is FDA-approved for major depression, but may be a good choice for extremely anxious patients

Table 3. CYP450 Isoenzyme Inhibition by the SSRIs

	1A2	2C9	2C19	2D6	3A4
Citalopram	+	0	0	+	0
Escitalopram	0	0	0	0	0
Fluoxetine	+	++	+ to ++	+++	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

Note: 0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition

Von Moltke et al., 2001; Greenblatt et al., 2002 ; Greenblatt et al., 1998.

as it causes fewer CNS activating effects. It also has few sexual side effects.⁹ It carries a black box warning, however, after over 30 cases of severe hepatotoxicity occurred worldwide.¹² However, the medication has been used in thousands of patients without problems, although patients who are at risk for liver problems should be monitored carefully. Nefazodone is metabolized through the C-P450, 3A4. It can interfere with the metabolism of other drugs that use this pathway including alprazolam.¹³ Nefazodone is relatively safe in overdose¹⁴ and discontinuation symptoms have been reported.^{15,16}

Venlafaxine (Effexor and Effexor XR) is a dual-agent reuptake agent with both serotonin and norepinephrine reuptake. It has FDA indications for MDD, generalized anxiety disorder (GAD) and social anxiety disorder (SAD). It does not inhibit or induce C-P450 and may have increased remission rates over SSRIs due to its dual-activity.¹⁷ Its side effects include nausea and constipation, headaches, sweating, and sexual side effects. Again, starting with a lower dose and increasing gradually may help minimize these. It also can cause hypertension in 5/100 patients at a total daily dose of less than 200 mg/day and in 13/100 patients at a dose greater than 200 mg/day. It has a short half-life, making discontinuation symptoms common with an abrupt taper.¹⁸ A second norepinephrine/serotonin reuptake inhibitor duloxetine (to be marketed as Cymbalta), is in the final stages of drug testing and is expected to be released sometime in 2004.

The mechanism of Bupropion (Wellbutrin, Wellbutrin SR and XL, and Zyban) is not entirely clear. It has dopaminergic and noradrenergic reuptake and it may be especially useful in treating reverse neurovegetative symptoms (poor energy, increased appetite, increased sleeping). Bupropion is marketed for use in smoking cessation and might be a good first-line choice for patients with both depression and nicotine dependence. Bupropion is a common augmentation agent when SSRIs fail.¹⁹ It has few C-P450 interactions. However, its activating effects may cause agitation, especially in anxious patients and it may

not be a good first-line agent for patients with anxiety disorders. Bupropion can cause GI side effects, headaches, and seizures in patients with risk factors for seizures. However, it has little potential for weight gain and sexual dysfunction. The new Wellbutrin XL formulation allows for convenient once-a-day dosing.

Mirtazapine (Remeron and Remeron sol-tab) has several mechanisms of action. First, it increases norepinephrine release on presynaptic alpha-adrenergic receptors. This in turn causes an increase in synaptic 5-HT levels. It also blocks 5-HT₂ and 3 receptors and it is an antagonist at histamine-1 receptors, especially at lower doses. It doesn't inhibit or induce C-P450 to a significant degree and may produce a response faster than SSRIs.²⁰ The sedative effects of mirtazapine may make it useful as a sleep aid and it may be useful in patients with significant anxiety.²¹ It lacks GI and sexual side effects,²¹ however its antihistamine-like effects can cause dry mouth, sedation, increased appetite, and weight gain. Use in higher doses to start (30 mg) may alleviate this somewhat as higher doses paradoxically have less antihistamine blockade. It also may increase cholesterol and triglyceride levels in patients.²² Mirtazapine is relatively safe in overdose.¹⁴

TRICYCLIC ANTIDEPRESSANTS AND MONOAMINE OXIDASE INHIBITORS

Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, desipramine, and clomipramine) are an older class of medications that are used less widely today. But they do have a role in treating patients with refractory depression and anxiety disorders and in treating migraine headaches and chronic neuropathic pain. Their use, however, has been limited by their side effects profile that includes dry mouth, constipation, orthostatic hypotension, sedation, urinary retention, and weight gain. Caution must be exercised in patients with a history of cardiac disease and arrhythmias as tricyclic antidepressants may cause cardiac conduction delays. Indeed, this effect can make tricyclic antidepressants quite lethal in overdose, limiting their use in patients with a history of medication overdose attempts. An EKG for all patients over 40 years of age or with a cardiac history is recommended prior to starting a tricyclic. Blood level monitoring is also necessary and with cardiac monitoring can offset the inexpensive cost of the generic tricyclics.

Monoamine oxidase inhibitors (MAOIs) are used even less frequently. Again, they may have a role in treating the refractory patient, but carry strict dietary restrictions and have a number of severe medication interactions that make them less tolerable and attractive to patients. Therefore their use is rare in a primary care setting.

ALGORITHMS

What should one do if the first trial of an antidepressant fails? First, assess for patient compliance. Second, assess if the medication has been tried for at least 4 weeks and, if so, increase the dose as tolerated to the maximum recommended dose. Third, assess comorbid medical and psychiatric conditions. Ask if the patient is abusing alcohol or drugs. Assess for underlying medical problems that might be contributing, such as hypothyroidism. Reassess if the psychiatric diagnosis is correct. Fourth, explore if the patient could benefit from psychotherapy along with medications and consider a referral to a therapist. After that, the next step is switching or augmenting the medication. Several treatment algorithms have been developed for treating major depressive disorder. These include the STAR²D project and the Texas Medication Algorithm Project.²³ The Texas Algorithm can serve as a general template for patients and is reproduced in Figure 1. After 2 or 3 failed medication trials, a referral to a psychiatrist for further evaluation and consultation is reasonable.

NEW FDA WARNINGS

The FDA recently added warnings to all of the antidepressants discussed above for both children and adults. These warnings caution about the possibility of antidepressants increasing agitation and possibly suicidal ideation and behavior. Unfortunately, since pharmaceutical companies have used varying criteria to define suicidal ideation, the true incidence is unknown. However, these medications have been marketed for over 15 years and have benefited millions of patients worldwide, with many lives saved.

Suicidal ideation is a common symptom of depression, and patients who are depressed may not act on their thoughts until they have more energy and motivation. One irony is that the older tricyclic antidepressants and MAOIs, which do not carry the new warnings, are more likely to be lethal in overdose. The newer antidepressants can cause agitation, and it is important to discuss this with patients prior to prescribing and to closely monitor patients for emergence of agitation. A general rule of starting at one-half of the target dose and increasing gradually helps reduce this. Patients should be seen in follow up within 2 weeks of an initial prescription to reassess suicidal ideation and side effects.

SUMMARY AND GENERAL GUIDELINES

Physicians have a wide variety of antidepressant options to utilize. The choice should be made based on a variety of factors including side effect profiles, cost, patient age, and comorbid conditions. Table 4 summarizes potential

Table 4. Summary of Potential Advantages and Disadvantages of Antidepressants

Antidepressants	Advantages	Disadvantages
Fluoxetine	Long-acting	Most P450 interactions
	Most studied	Agitation
	Rare withdrawal symptoms	Sexual side effects
	Generic available	
Sertraline	Less sedating	GI side effects Agitation Sexual side effects
Paroxetine	Sedating	Weight gain
	Generic available	Withdrawal symptoms Sexual side effects
Citalopram/ Escitalopram	Fewer P450 interactions	Sexual side effects
Venlafaxine	Dual-action may be more efficacious	Withdrawal symptoms Sexual side effects Hypertension
Bupropion	Smoking cessation	Agitation
	Fewer sexual side effects	Seizures
	Energy activating	Headaches
Nefazodone	Generic	
	Sedating	Rare liver impairment
	Fewer sexual side effects	P450 interactions
	Generic	Withdrawal symptoms
Mirtazapine	Less agitation	
	Hypnotic	Weight gain
	Less agitation	Sedation
	Fewer sexual side effects	

advantages and disadvantages of these antidepressants. No matter the choice, it is important to monitor patients carefully during the acute phase of treatment and to advocate that patients remain on the medications for the recommended 6-9 months to prevent relapse. Patients also need to be counseled to taper their medications gradually to avoid withdrawal effects. Depression is a complex, yet very treatable illness, and identifying and adequately treating all affected patients is the goal.

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