SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Antidepressants improve depression symptoms in adults compared with placebo. Among antidepressants, there are not important differences in effectiveness.	A	7, 16
Treat depression at adequate doses of antidepressants for a minimum of four to eight weeks before labeling a treatment regimen ineffective.	C	14
Monitor patients taking antidepressants for side effects, suicidality, and effectiveness.	C	14
Consider a change in therapy if there is no improvement after four to 12 weeks of antidepressant treatment.	B	21
After treatment failure with an antidepressant, the next option may be a different medication of the same class, a medication from a different class, or augmentation with a second agent.	B	14, 21, 27

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 739 or http://www.aafp.org/afpsort.xml.

dopamine neurotransmitter receptors.[9] TCAs block norepinephrine reuptake pumps and, to varying degrees, serotonin reuptake pumps. Their actions upon acetylcholine, histamine, and adrenergic receptors frequently cause unwanted side effects (e.g., weight gain, sedation, constipation, dry mouth, orthostatic hypotension, reflex tachycardia). These side effects are less pronounced with secondary amine TCAs (e.g., nortriptyline [Pamelor], desipramine [Norpramin]) than with tertiary amines (e.g., imipramine [Tofranil], amitriptyline [Elavil; brand no longer available in the United States]).[10]

TCAs are metabolized primarily by the hepatic cytochrome P450 enzymes. Genetic variations in P450 enzyme activity result in wide variations in TCA blood levels among persons taking the same dosage.[10] The recommended starting and maintenance dosages for TCAs were developed empirically and are not based on strong clinical evidence. One review found lower dosages of TCAs (i.e., 75 to 100 mg per day or less) to be equally as effective as standard dosages with fewer side effects.[11]

Compared with SSRIs, the use of TCAs is associated with a higher risk for significant cardiovascular events in patients with ischemic heart disease.[12] Furthermore, TCAs are highly lethal in overdose relative to SSRIs. TCA overdose can cause respiratory depression, cardiac arrhythmias, hypothermia, seizures, hallucinations, and hypertension for as long as five days.[4]

SSRIs AND SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

SSRIs rapidly became the most popular treatment for depression in the United States, beginning with the introduction of fluoxetine (Prozac) in 1986. SSRIs act by inhibiting presynaptic serotonin reuptake. The SNRIs venlafaxine (Effexor) and duloxetine (Cymbalta) inhibit serotonin and norepinephrine reuptake at higher doses.[9]

Side effects of serotonin reuptake inhibition may include agitation, insomnia, gastrointestinal disturbances (e.g., nausea, diarrhea), and male and female sexual dysfunction.[10] Medications that act upon serotonin increase the risk of gastrointestinal hemorrhage. In one study, patients who took SSRIs had a risk of gastrointestinal hemorrhage that was 3.6 times higher than control groups (confidence interval [CI], 2.7 to 4.7), resulting in an additional 3.1 hemorrhages per 1,000 patient-years. The combination of SSRIs with low-dose aspirin or nonsteroidal anti-inflammatory drugs further increases this risk.[13]

SSRIs are primarily metabolized through the cytochrome P450 system. Interactions are possible with a wide variety of medications, including benzodiazepines, antipsychotics, antiarrhythmics, and phenytoin (Dilantin). Of the SSRIs, fluvoxamine (Luvox, brand no longer available in the United States), fluoxetine, and paroxetine (Paxil) are the most prone to cause drug-drug interactions because they inhibit the metabolism of other medications through the P450 system, and these three medications dramatically increase TCA levels. Other medications that act upon serotonin have a lower risk of drug-drug interactions, but still may elevate TCA levels. For example, the SNRIs venlafaxine and duloxetine raise TCA levels dramatically, and the anti-infective medication ciprofloxacin (Cipro) may dramatically increase duloxetine levels.[10]

OTHER ANTIDEPRESSANTS

Bupropion (Wellbutrin) inhibits the presynaptic reuptake of norepinephrine and dopamine. Trazodone (Desyrel, brand no longer available in the United States), nefazodone (Serzone, brand no longer available in the United States), and mirtazapine (Remeron) selectively block the 5-HT2A and 5-HT2C serotonin receptors. In addition, mirtazapine enhances the neurotransmission of serotonin and norepinephrine by blocking α-2 adrenergic receptors. Bupropion interacts with TCAs, some SSRIs (e.g., fluoxetine, paroxetine, sertraline [Zoloft]), antipsychotics, antiarrhythmics, selegiline (Eldepryl), amantadine (Symmetrel), and metoprolol (Toprol-XL). It lowers the seizure threshold in a dose-dependent fashion.[4] Mirtazapine interacts with clonidine (Catapres) and diazepam (Valium). Trazodone and nefazodone interact with an extensive list of medications. Nefazodone may rarely cause fulminant hepatic failure.[4,9] Monoamine oxidase inhibitors (MAOIs) are potent antidepressants, but their need for dietary restrictions and potential for fatal drug-drug interactions make them unfavorable as a first-line treatment.

Some persons may use *Hypericum perforatum* (St. John's wort) as an alternative to prescription antidepressants. However, randomized controlled trials of its effectiveness in patients with mild to moderate depression have had conflicting results and, although it appears to be more effective than placebo, the benefits are small. It affects multiple cytochrome P450 pathways and, therefore, has considerable potential for drug-drug interactions.[14,15]

DIFFERENCES AMONG ANTIDEPRESSANTS

The differences in effectiveness appear to be small among the antidepressant classes and the medications in each class.[16] Amitriptyline may be slightly more effective than other antidepressants (CI, 1.01 to 1.23; odds ratio = 1.12; NNT = 50), but causes more side effects.[17] Data from meta-analysis suggest fluoxetine may be slightly less effective than other antidepressants.[5] Mirtazapine has a slightly faster onset of action than SSRIs and may cause less sleep disturbance, but also may cause more weight gain.[5] Compared with SSRIs, some, but not all, trials showed more early-responders to venlafaxine; however, it is associated with elevations in diastolic blood pressure and increased dizziness, nausea, and vomiting compared with SSRIs.[5] Bupropion may have fewer sexual side effects than SSRIs, and appears to induce a modest weight loss, but has a higher incidence of insomnia and headache.[5] Of the SSRIs, paroxetine is associated with the greatest amount of weight gain, and fluoxetine with the least.[5]

Compared with TCAs and MAOIs, the primary advantages of the newer classes of antidepressants are their safety and tolerability. The use of an SSRI or SNRI instead of a TCA doubles the likelihood that a patient will complete 90 days of treatment.[18]

Treatment Considerations

The choice of initial treatment with antidepressants should be based on safety, anticipated side effects *(Table 1[4])*, and cost *(Table 2[4,19,20])*. SSRIs, SNRIs, or bupropion are reasonable choices for initial treatment, whereas less sedating TCAs (e.g., desipramine, nortriptyline) may be acceptable for some patients.[14] Monitoring should be more frequent immediately after treatment onset and after changes in treatment. The frequency with which patients are evaluated after initiation of treatment depends on the characteristics of the individual patient, and monitoring should focus on side effects, effectiveness, and suicidality. An adequate trial consists of four to eight weeks of treatment. Adjustments in dosage should be made as needed and tolerated. A change in treatment should be considered for patients who have not improved after four to 12 weeks of treatment.[14] Once remission is achieved, treatment should be continued at the same dose for at least six to 12 months to prevent relapse.[21] The decision of when to terminate treatment is based on the patient's risk of recurrence. A history of recurrent depression, concurrent psychiatric illness, persistent symptoms, and the presence of other medical illnesses indicate an increased likelihood of relapse.[14] Tapered withdrawal of SSRIs and SNRIs is necessary to prevent an unpleasant discontinuation syndrome *(Table 3[22])*; the risk of this is highest with paroxetine and venlafaxine.[23]

TREATMENT CHANGES

When the response to treatment is inadequate, changing to a medication within the same class or to one in a different class, or augmenting with a second drug *(Table 4[19,20,24])* would be acceptable choices.[14] Genetically determined differences in drug metabolism may cause notable variations in patients' blood levels with most antidepressants.[23] Desipramine is an extreme example, with up to a 50-fold difference in blood levels among patients taking the same amount of medicine.[25] A large, recent trial randomized patients who did not achieve remission with citalopram to sertraline, extended-release venlafaxine (Effexor XR), or sustained-release bupropion (Wellbutrin SR). All were equally well-tolerated and effective, and in each case an additional one in four patients achieved remission.[26,27] Intolerance or lack of response with one SSRI does not predict intolerance

Table 1. Side Effects of Selected Antidepressants

Type of side effect	*SSRIs*	*SNRIs*	*Trazodone (Desyrel)**	*Bupropion (Wellbutrin)*
Cardiovascular	Prolonged QT interval	Elevated blood pressure	Dysrhythmia, hypertension, hypotension	Dysrhythmia, elevated blood pressure, tachycardia
Dermatologic	Rash, sweating	Diaphoresis	Sweating	Itching, rash, Stevens-Johnson syndrome, urticaria
Endocrine metabolic	—	—	Weight gain	Weight loss
Gastrointestinal	Dyspepsia, hemorrhage, loss of appetite, nausea, xerostomia	Constipation or diarrhea, decreased appetite, gastritis, nausea, xerostomia	Constipation, diarrhea, loss of appetite, nausea, vomiting, xerostomia	Constipation, disorder of taste, nausea, pharyngitis, xerostomia
Hematologic	—	—	Hemolytic anemia, leukocytosis, methemoglobinemia	—
Musculoskeletal	—	—	—	Arthralgia, myalgia
Neurologic	Asthenia, insomnia, seizure, somnolence, tremor	Dizziness, fatigue, insomnia, somnolence	Dizziness, headache, insomnia, lethargy, memory impairment, seizure, somnolence	Confusion, dizziness, headache, insomnia, seizure, tinnitus, tremor
Ophthalmic	—	Blurred vision	Blurred vision	—
Psychiatric	Mania/hypomania, suicidal thoughts, suicide, worsening of depression	Suicidal thoughts, suicide, worsening of depression	Suicidal thoughts, suicide, worsening of depression	Agitation, anxiety, hostility, mania, psychosis, suicidal thoughts, worsening of depression
Renal	—	Dysuria	—	—
Reproductive	Abnormal ejaculation, impotence	Abnormal ejaculation, impotence	Priapism	—

SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin norepinephrine reuptake inhibitors.

**—Brand no longer available.*

Information from reference 4.

or ineffectiveness with other SSRIs.[26] Augmentation with bupropion SR or the anti-anxiety agent buspirone (Buspar) to an SSRI increases the remission rate by 30 percent.[27] Bupropion SR provides better symptom relief and has fewer side effects than buspirone.[27] There is limited evidence for using lithium, anticonvulsants, thyroid hormone, and other combinations of antidepressants in treatment-resistant depression.[19,21] The atypical antipsychotics have antidepressant-like activity, and several are potent serotonin receptor antagonists. Most studies show improved response and remission rates when used in combination with SSRIs.[28,29] The potential benefits of these medications must be weighed against the high risk of long-term weight gain and metabolic abnormalities.[30]

IMPROVING ADHERENCE TO TREATMENT

Risk factors for treatment failure *(Table 5*[19,31]*)* include patient nonadherence, which occurs early on in approximately 40 percent of the American adults who

Table 2. Dosages and Costs of Selected Antidepressants

Medication	*Typical dosage range per day*	*Cost**	*Lower dose in renal/liver diseases*
Selected SSRIs			
Citalopram (Celexa)	20 to 60 mg	$9 to 78† (20 mg, #30)	No/yes
Escitalopram (Lexapro)	10 to 20 mg	81 (10 mg, #30)	No/yes
Fluoxetine (Prozac)	20 to 80 mg	9 to 80† (20 mg, #30)	No/yes
Paroxetine (Paxil, Paxil CR)	20 to 50 mg (25 to 62.5 mg [CR])	50 to 82† (20 mg, #30), 104 (25 mg [CR], #30)	Yes/yes
Sertraline (Zoloft)	50 to 200 mg	13 to 86† (50 mg, #30)	No/yes
SNRIs			
Duloxetine (Cymbalta)	30 to 90 mg	121 (30 mg, #30)	Yes/avoid
Venlafaxine, extended release (Effexor XR)	37.5 to 225 mg	110 (75 mg, #30)	Yes/yes
Other second-generation antidepressants			
Bupropion SR (Wellbutrin SR)	100 to 200 mg, twice daily	94 to 120† (150 mg, #60)	Yes/yes
Bupropion XL (Wellbutrin XL)	150 to 450 mg	164† (300 mg, #30)	Yes/yes
Mirtazapine (Remeron)	15 to 45 mg	78 to 81† (15 mg, #30)	Yes/yes
Nefazodone (Serzone, brand no longer available in the United States)	100 to 300 mg, twice daily	92† (100 mg, #60)	No/‡
Trazodone (Desyrel, brand no longer available in the United States)	150 to 600 mg	44 to 85† (150 mg, #30)	No/yes
Selected TCAs			
Amitriptyline (Elavil, brand no longer available in the United States)	25 to 300 mg	1 to 19† (50 mg, #30)	No/yes
Imipramine (Tofranil)	25 to 200 mg	2 to 37† (50 mg§, #30)	No/yes
Nortriptyline (Pamelor)	25 to 150 mg	24† (25 mg, #30)	Yes/yes

SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

**—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in* Red Book. *Montvale, N.J.: Medical Economics Data, 2007. Cost to the patient will be higher, depending on prescription filling fee.*

†—*Denotes generic.*

‡—*Contraindicated if history of nefazodone-induced liver disease. Precaution in active liver disease. Black box warning for hepatotoxicity.*

§—*The brand name of this medication is no longer available in 50-mg tablets.*

Information from references 4, 19, and 20.

discontinue antidepressant medication during their first month of treatment.[18] Predictors of early discontinuation include a lower education level, lower family income, and ethnicity. Patients who concurrently receive psychotherapy are more likely to continue antidepressant therapy.[18] Benzodiazepines taken in combination with antidepressants in the first few weeks also may reduce the risk of early treatment discontinuation.[32]

Continued contact with the treating physician benefits some patients after recovery. A study of primary care patients who had complete symptom resolution with an antidepressant found that those who received two additional physician visits and three phone calls in a one-year period had fewer depressive symptoms and were more likely to purchase their medication, but did not experience fewer relapses.[24]

Table 3. Symptoms of SSRI Discontinuation Syndrome

Anxiety	Insomnia
Ataxia	Irritability
Diarrhea	Nausea
Dizziness, vertigo, or light-headedness; feeling "faint"	Paresthesias or "electric shock" sensations
Fatigue	Tremor
Headache	Visual disturbances
	Vomiting

SSRI = selective serotonin reuptake inhibitor.

Information from reference 22.

Table 4. Selected Medications Used for Depression Treatment Augmentation

Medication	*Typical dosage range per day*	*Cost**	*Lower dose in renal/ liver disease*
Antidepressants			
Bupropion SR (Wellbutrin SR)	100 to 200 mg, twice daily	$94 to 120† (150 mg, #60)	Yes/yes
Trazodone (Desyrel, brand no longer available)	50 to 600 mg	44 to 85† (150 mg, #30)	No/yes
Atypical antipsychotics			
Aripiprazole (Abilify)	10 to 30 mg	393 (10 mg, #30)	No/no
Olanzapine/fluoxetine (Symbyax)	6 mg/25 mg	295 (6 mg/25 mg, #30)	No/yes
Olanzapine (Zyprexa)	5 to 20 mg	246 (5 mg, #30)	No/no
Quetiapine (Seroquel)	50 to 800 mg	107 (50 mg, #30)	No/yes
Risperidone (Risperdal)	0.25 to 6 mg	120 (0.5 mg, #30)	Yes/yes
Ziprasidone (Geodon)	20 to 80 mg twice daily	331 (20 mg, #60)	No/yes
Other agents			
Buspirone (Buspar)	5 to 30 mg three times daily	27 to 76† (5 mg, #90)	Yes/yes
Lamotrigine (Lamictal)	25 to 300 mg	192† (25 mg, #60)	Yes/yes
Levothyroxine	50 to 100 mcg	9 to 10† (50 mcg, #30)	No/no
Liothyronine (Cytomel)	25 to 50 mcg	29 (25 mcg, #30)	No/no
Lithium	600 to 900 mg per day divided	16 to 19† (300 mg, #90)	Yes/no

NOTE: *Augmentation therapy or antidepressants used in combination are not approved by the U.S. Food and Drug Administration as treatment strategies.*

**—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in* Red Book. *Montvale, N.J.: Medical Economics Data, 2007. Cost to the patient will be higher, depending on prescription filling fee.*

†—Denotes generic.

Information from references 19, 20, and 24.

SEROTONIN SYNDROME

Serotonin syndrome is precipitated by medications that act as serotonin agonists. It can be induced by antidepressants and a wide assortment of other drugs. Combining serotonergic drugs is particularly risky. It usually begins within hours of initiation or change in dosage of a medication, but may occur weeks after discontinuing fluoxetine or MAOIs.[33] *Table 6* lists the symptoms of serotonin syndrome.[33]

SUICIDE RISK

Patients with depression have a risk of suicide that is 20 times above normal.[34] The short-term risk of suicide is not decreased by antidepressants, which may actually increase this risk. The U.S. Food and Drug Administration issued a black box warning regarding increased suicidal ideation and behaviors in children, adolescents, and young adults (18 to 24 years of age) treated with antidepressants (http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf). A retrospective analysis of older patients showed the risk of suicide to be five times higher in the first month of treatment with an SSRI compared with patients treated with other antidepressants.[34] However, a large meta-analysis found only a

Table 5. Risk Factors for Depression Treatment Failure

Addiction	History of physical or sexual abuse
Coexisting medical illness	Inadequate medication dose
Coexisting psychiatric illness	Inadequate treatment duration
Cognitive impairment	Incorrect diagnosis
Family history of treatment failure	Severity of depression
Genetic polymorphisms in serotonin transporter proteins	Treatment nonadherence

Information from references 19 and 31.

Table 6. Symptoms of Serotonin Syndrome

Akathisia	Dilated pupils	Seizures
Anxiety	Muscular rigidity	Sweating
Clonus	Renal failure	Tachycardia
Delirium	Rhabdomyolysis	Tremor

Information from reference 33.

trend toward self-harm that did not meet statistical significance.[35] Treatment with antidepressants for patients who have unrecognized bipolar disorder may result in worsening of symptoms.[14] Based on these concerns, close follow-up and monitoring for suicidal ideation, agitation, mania, and psychosis is important for all patients, particularly when initiating treatment.

NONPHARMACOLOGIC TREATMENT OF DEPRESSION

Medication may not be desired, tolerated, or appropriate for every patient experiencing depression. Current evidence supports the effectiveness of counseling in the treatment of depression, and a recent meta-analysis suggests that the combination of psychotherapy and medication is more effective than medication alone.[36] Meta-analyses have shown cognitive behavior therapy to have effectiveness similar to antidepressant medication for patients with mild to moderate depression,[37] as well as for severely depressed outpatients.[38] Cognitive behavior therapy also has value for relapse prevention.[39,40] A recent meta-analysis suggests interpersonal therapy to be as effective as medication.[41]

Electroconvulsive therapy remains an effective treatment for depression, but its effects do not persist with time, and concerns about cognitive impairment make it an unpopular treatment choice. In patients who are morbidly depressed and refractory to other treatments, electroconvulsive therapy may dramatically improve symptoms when no other treatment has worked.[21]

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