CLINICAL REVIEW

The Pharmacologic Treatment of Depression

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Background. **Family physicians often provide the first line of treatment for patients with depression. Many effective drugs are now available for the pharmacologic treatment of depression.**

Methods: **We searched MEDLINE from 1991-96 under the topics of depressive disorders/treatment and antidepressant medications. Other sources were found by back-referencing from these references and from pharmacology texts.**

Results: **Although antidepressants appear to be equally effective, selective serotonin reuptake inhibitors are frequently the drugs of choice because of their safety profile and less troublesome side effects.**

Conclusions: **When prescribing antidepressant medications, the clinician must educate patients about potential side effects and about the amount of time that must be allowed for therapeutic efficacy. Drug interactions and concurrent medical conditions are important factors in the choice of an antidepressant.**
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Depression is a common finding in primary care practice, with a 6-month prevalence of 5.8 percent and a lifetime prevalence of 17 percent in the United States.[1] Detection has been discussed elsewhere.[2] Once the diagnosis has been made, the physician must determine the optimal treatment plan for each patient. In cases of mild depression, psychotherapy alone can be effective, but in moderate to severe depression, pharmacotherapy with an antidepressant medication is indicated, regardless of whether the patient is referred for psychotherapy.[3]

Methods

The authors searched MEDLINE from 1991 through 1996 using the key words "depression/therapy" and "antidepressive agents" and reviewed current pharmacology and psychiatry textbooks regarding the available antidepressants in the United States, with attention to potential side effects, drug interactions, and special considerations in treating depressed patients who have concurrent medical illnesses. Earlier references were obtained by back-referencing and from the authors' files. The purpose of this review is to summarize clinically useful information for primary care physicians who are treating major depressive disorders with medication.

Classes of Antidepressants

A large selection of drugs is available in the United States for the treatment of depression (Table 1). Since all are effective, selection of a drug is based on considerations of safety, tolerability, cost, and convenience of dosing. Potential drug interactions and concurrent medical conditions also guide the selection of an appropriate antidepressant.

Selective Serotonin Reuptake Inhibitors

In the 1990s the drugs of choice for many patients for the treatment of major depressive disorder have been the selective serotonin reuptake inhibitors (SSRIs), fluoxetine, paroxetine, and sertraline, because they have favorable safety profiles and are easy to administer.[4,5] They are not lethal in overdose, and patients are less likely to drop out of treatment because of adverse effects. Dosage titration is not usually necessary. Fluvoxamine, also an SSRI, has been approved for use in obsessive-compulsive disorder as well as depression.

Side effects of SSRIs are generally milder than those of the older classes of antidepressants.[6] Common side effects are listed in Table 2. Nausea, common during the first week, tends to wane as the patient develops tolerance. Fluvoxamine has side effects similar to those of the other SSRIs[7] except there may be less nausea.[8] Because in-

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Table 1. Antidepressants Currently Available in the United States.

Generic Name	Brand Name	Adult Dosage/24 hr	Interval	Cost $*
Selective serotonin reuptake inhibitors				
Fluoxetine	Prozac	10-80 mg	qd	71-280
Paroxetine	Paxil	10-50 mg	qd	59-127
Sertraline	Zoloft	50-200 mg	qd	65-133
Fluvoxamine	Luvox	50-300 mg	qd or bid	65-134
Tricyclic antidepressants				
Amitriptyline	Elavil, others	50-300 mg	qd	20-106 3-14†
Amoxapine	Asendin	100-400 mg	qd or divided	65-260 44-176†
Desipramine	Norpramine	50-300 mg	qd or bid	25-178 14-139†
Doxepin	Adapin Sinequan	50-300 mg	qd or divided	17-118 5-32†
Imipramine	Tofranil, others	50-300 mg	qd	24-125 2-12†
Nortriptyline	Pamelor Aventyl	50-200 mg qd	qd or divided	59-361 43-260†
Protriptyline	Vivactil	15-60 mg	tid or qid	45-131 37-105†
Trimipramine	Surmontil	50-300 mg	divided or hs	35-154
Tetracyclic antidepressants				
Maprotiline	Ludiomil	50-225 mg	qd or divided	22-88 15-64†
Monoamine Oxidase Inhibitors				
Phenelzine	Nardil	15-90 mg	qd	13-78
Tranylcypromine	Parnate	10-40 mg	qd	15-60
Atypical antidepressants				
Bupropion	Wellbutrin SR	200-450 mg	bid	71-116
Mirtazapine	Remeron	15-45 mg	qd	59-121
Nefazodone	Serzone	200-600 mg	bid	61-91
Trazodone	Desyrel, others	150-500 mg	divided	62-335 25-65†
Venlafaxine	Effexor	75-375 mg	bid or tid	63-144

*Average wholesale price to pharmacist for 30-day supply at lowest to highest dosage range, rounded to the nearest dollar, from the First Databank, June 1997. Price to patient will be higher.
†Generic price when available.

somnia can be a problem, these activating antidepressants are usually administered in the morning. Jitteriness must be differentiated from worsening anxiety, antidepressant-induced akathisia, nocturnal myoclonus, and hypomania or mania. Management includes waiting for tolerance to develop, dosage reduction, and changing antidepressants.[9] Patients taking sertraline and paroxetine might experience considerable improvement in sexual function with scheduled weekend drug holidays. Short holidays are not effective with fluoxetine because it has a longer half-life.[10] Anorgasmia may be managed by waiting for tolerance to develop, dosage reduction, treatment with the serotonergic antihistamine cyproheptadine,[11] or prescribing a different antidepressant, such as bupropion.

Drug interactions with SSRIs are listed in Table 3. The combination of SSRIs with monoamine oxidase inhibitors (MAOIs) has resulted in

Table 2. Common Side Effects and Frequency of Selective Serotonin Reuptake Inhibitors.

Fluoxetine (Prozac)	Percent*	Sertraline (Zoloft)	Percent*	Paroxetine (Paxil)	Percent*
Nausea	21	Nausea	26	Nausea	26
Headache	20	Headache	20	Somnolence	23
Nervousness	15	Diarrhea/loose stools	18	Dry Mouth	18
Insomnia	14	Insomnia	16	Headache	18
Diarrhea	12	Dry Mouth	16	Asthenia	15
Drowsiness	12	Male sexual dysfunction (ejaculatory delay)	15	Constipation	14
Anxiety	9	Somnolence	13	Dizziness	13
Anorexia	9	Dizziness	12	Insomnia	13
Increased sweating	8	Tremor	11	Ejaculatory disturbance	13
		Fatigue	11		
Discontinued (side effects)	15	Discontinued (side effects)	15	Discontinued (side effects)	21

*Rounded to the nearest 1%.

many adverse events, including the serotonin syndrome, which is characterized by such mental status changes as hypomania and confusion, and physical symptoms, such as myoclonus, hypertension, tremor, and diarrhea.[12] Death has resulted in some cases.[13] SSRIs inhibit the cytochrome P-450 2D6 and other enzyme systems in the liver, resulting in altered metabolism of a number of other drugs. Paroxetine and fluoxetine are the most potent inhibitors. Sertraline is less active. Desipramine, nortriptyline, and venlafaxine are also substrates of cytochrome P-450 2D6.[14] Fluoxetine is also a potent inhibitor of the cytochrome P-450 2C9 enzyme system and has been reported to block analgesia from opiates, such as morphine.[15] Significantly increased half-lives of tricyclic antidepressants,[16] clozapine,[17] carbamazepine,[18] alprazolam,[19] diazepam,[20] and haloperidol[21] have been reported when these drugs are given concurrently with SSRIs. Lower doses of the affected agent might be required. Although the cytochrome P-450 3A3/4 enzyme system is inhibited by SSRIs, their potency is much less than that of ketoconazole, itraconazole, and erythromycin. Fluvoxamine is contraindicated with terfenadine (Seldane) and astemizole (Hismanal) and should be avoided with clozapine and cisapride.

The most important difference among the three SSRIs lies in their pharmacokinetics. Fluoxetine has a significantly longer half-life, 84 hours, compared with 21 hours for paroxetine and 26 hours for sertraline. Fluoxetine also has an active metabolite, norfluoxetine, that has an elimination half-life of 146 hours (range 77 to 235 hours). It is necessary to wait at least 5 weeks between discontinuing fluoxetine and starting an MAOI and at least 14 days for other SSRIs.

SSRIs are also prescribed for obsessive-compulsive disorder, panic disorder, and premenstrual syndrome. Fluoxetine is the only SSRI available in liquid form. Although SSRIs cost more than many older antidepressants, drugs are only a small part of the cost of treating depression. An overall reduction in direct cost has been shown with the SSRIs compared with tricyclic antidepressants.[22]

Mixed Serotonin-Norepinephrine Inhibitors

Tricyclic antidepressants (TCAs) are the most studied class of antidepressants because they have been in use longer. TCAs and SSRIs are equivalent in efficacy for the treatment of major depression. A list of common side effects of TCAs is found in Table 4. Anticholinergic effects, weight gain, sedation, and orthostatic hypotension are most troubling with the tertiary amine tricyclic medications, which include amitriptyline, clomipramine, doxepin, imipramine, and trimipramine. The secondary amine tricyclic medications—amoxapine, desipramine, maprotiline, nortriptyline, and protriptyline—cause less sedation and fewer anticholinergic effects.

TCAs are toxic in overdose, and patients at risk for suicide must be given limited amounts to avoid the potential for suicide. A potentially lethal TCA dose for an adult is only three to five times the therapeutic dose, or a 1-week supply of the antidepressant. For a child the toxic dose is far less.

Table 3. Drug Interactions With Selective Serotonin Reuptake Inhibitors.

Drug	Interaction	Response
Contraindicated		
MAOIs	Potentially fatal serotonin syndrome	Do not use
Terfenadine (Seldane)	Possible cardiovascular toxicity	Avoid
Use with caution		
Class I antiarrhythmics propafenone, flecainide	Increase levels of antiarrhythmics	Might require lower dose of antiarrhythmic
Antidepressants	SSRI may increase levels of TCAs and trazodone	Use lower doses
Benzodiazepines	Increased half-life of some benzodiazepines	Monitor sedation
Buspirone	Decreased effect of buspirone	Increase buspirone or change anxiolytic
Carbamazepine	Increased half-life of carbamazepine	Monitor carbamazepine level
Cimetidine	Increased levels of SSRI	Might need lower dose of SSRI
Clozapine	Increases clozapine effects and toxicity	Lower clozapine dose
Coumadin	Increased prothrombin time	Monitor APTT
Dextromethorphan	Hallucinations	Avoid
Digoxin	Increased digoxin levels	Monitor digoxin levels
Haloperidol	Increased half-life of haloperidol	Monitor symptoms
Phenobarbital	Decreased levels of SSRI	Increase dose of SSRI
Phenytoin	Decreased levels of SSRI	Increase dose of SSRI
Tolbutamide	Increased levels of tolbutamide	Monitor glucose
Tramadol (Ultram)	Possible arrhythmias	Avoid
Tryptophan	Agitation, restlessness, GI toxicity	Avoid

MAOI - monoamine oxidase inhibitor, SSRI - selective serotonin reuptake inhibitor, TCA - tricyclic antidepressant, APTT - activated partial thromboplastin time, GI - gastrointestinal.

Signs of toxicity include coma, seizure, arrhythmias, tachycardia, hypotension, and confusion.[23] When TCAs are prescribed with other medications, patients must be monitored for signs of toxicity as a result of increased levels of drug. Reported drug interactions are listed in Tables 5 and 6. TCAs are contraindicated with monoamine oxidase inhibitors and should be used with caution with a number of other drugs, including class I antiarrhythmic medications, such as quinidine, flecainide, and propafenone.

TCAs are also prescribed for chronic pain, fibromyalgia, chronic fatigue syndrome[24,25] and attention deficit hyperactivity disorder in children. Amitriptyline and imipramine can be administered intramuscularly. Doxepin and nortriptyline are available in oral solutions.

Venlafaxine is reported to be effective in treating severe, melancholic depression that has been unresponsive to other agents. Common side effects include nausea (37 percent), somnolence (23 percent), dry mouth (22 percent), dizziness (19 percent), constipation (15 percent), nervousness (13 percent), asthenia, sweating, tremor, and abnormal ejaculation or orgasm.[26] Because dose-related sustained diastolic hypertension has been reported, this drug is usually reserved for patients unresponsive to first-line antidepressants.[27] Venlafaxine is a substrate of the cytochrome P-450 2D6 system. Such drugs as quinidine and SSRIs can increase serum concentration of venlafaxine. Cimetidine reduces clearance of venlafaxine.

Mixed Serotonin Effects

Trazodone was the first antidepressant developed that was not lethal when overdosed. It is very sedating, which can be beneficial for patients suffering from insomnia caused by their depression, and is sometimes used along with an SSRI in patients who have difficulty sleeping.[28] It has fewer anticholinergic side effects than many of the tricyclic antidepressants, but it can cause postural hypotension, especially in the elderly, and it has been associated with priapism in a small percentage of men and with arrhythmias in those with preexisting heart disease. Increases in serum levels of digoxin and phenytoin have been reported when these drugs are given with trazodone.[29]

Table 4. Tricyclic and Tetracyclic Antidepressants Grouped According to Frequency of Side Effects.

Side Effect	Common	Intermediate	Low	Not Reported
Anticholinergic effects	Amitriptyline Doxepin Imipramine	Protriptyline Amoxapine Maprotiline	Desipramine Nortriptyline Trimipramine	
Sedation	Amitriptyline Doxepin Imipramine Trimipramine Maprotiline	Amoxapine	Desipramine Protriptyline	
Insomnia/Agitation		Amoxapine	Protriptyline Imipramine Desipramine	Amitriptyline Doxepin Nortriptyline Trimipramine Maprotiline
Orthostatic hypotension	Amitriptyline Imipramine	Desipramine Doxepin Nortriptyline Protriptyline Trimipramine Maprotiline Amoxapine		Maprotiline
Cardiac arrhythmias	Amitriptyline Amoxapine Imipramine	Desipramine Doxepin Nortriptyline Protriptyline Trimipramine	Maprotiline	
Weight gain (> 6 kg)	Amitriptyline Doxepin Imipramine Trimipramine	Maprotiline	Amoxapine Desipramine Nortriptyline	Protriptyline
Sexual dysfunction		Amitriptyline Doxepin Imipramine	Desipramine Nortriptyline Protriptyline Trimipramine	

Nefazodone is chemically related to trazodone, but appears to have a more favorable side-effect profile[30] It differs from the SSRIs in that sexual dysfunction is not reported. α-Adrenergic activity is only slight, and there is virtually no cardiotoxicity. Anticholinergic activity and histaminergic activity are less than with other antidepressants.[31] Side effects include somnolence, dizziness, dry mouth, nausea, constipation, headache, and amblyopia.[32] Nefazodone is a potent inhibitor of the cytochrome P-450 3A4 isoenzymes and is contraindicated with terfenadine (Seldane), astemizole (Hismanal), MAOIs (Nardil, Parnate), and cisapride (Propulsid). If coadministered with triazolam or alprazolam, the benzodiazepine doses might need to be reduced. Lorazepam does not appear to be affected. Other cytochrome P-450 substrates that might be affected include calcium channel blockers and tamoxifen.[33]

Mixed Norepinephrine-Dopamine Reuptake Inhibitors

The effectiveness of bupropion in the treatment of depression is similar to that of the SSRIs and TCAs, and its efficacy has been shown in patients previously unresponsive to TCAs. Bupropion has recently been approved for use as an aid in smoking cessation.[34]

Causing little orthostatic hypotension and no anticholinergic effects or sexual dysfunction, bupropion appears to be safe in patients with preexisting heart disease.[35] Side effects can include agitation and insomnia, psychosis, confusion, and weight loss. Although not lethal in overdose, bupropion might lower the seizure threshold,[36] and is contraindicated in patients with seizure disorders. At least 14 days should elapse from the discontinuation of an MAOI before initiating treatment with bupropion. Bupropion should be used with extreme caution in patients taking levodopa.

Table 5: Interactions With Monoamine Oxidase Inhibitors.

Food*	Drugs	Adverse Effects
Aged cheeses (Boursault, Brie, Camembert, Cheddar, Emmenthaler, Gruyere, mozzarella, Parmesan, Romano, Roquefort, and Stilton); beer, red wine; broad beans; caviar, anchovies; chicken or beef liver; smoked meats (bologna, pepperoni, salami, summer sausage); yeast products	Antidepressants (TCAs, SSRIs); levodopa; lithium; sympathomimetics (eg, amphetamines, ephedrine, metaraminol, phenylephrine, phenylpropanolamine, pseudoephedrine)	Hypertensive crisis; arrhythmias; severe headache; death
	CNS depressants, including anesthetic agents, meperidine, morphine, barbiturates, codeine	Hypotension
	Thiazide diuretics	Can potentiate hypotensive effect
	Phenothiazines	Hypotension and increased extrapyramidal effects
	Insulin	Increased hypoglycemic reactions

*Foods containing tyramine and other amines, often as a result of aging or fermenting.

Monoamine Oxidase Inhibitors

Despite being effective antidepressants, the monoamine oxidase inhibitors (MAOIs) phenelzine and tranylcypromine are infrequently used because of the risk of toxic interactions with many foods and drugs (Table 5). Foods containing high levels of tyramine, such as aged cheeses, the brine from pickled herring, beers, wine, liver, yeast extract, dry sausages, and fava beans, can lead to a hypertensive crisis. Excessive amounts of caffeine and chocolate should be avoided. MAOIs prolong and potentiate the effects of sympathomimetic amines, which are found in many over-the-counter cold preparations. Concurrent administration can result in extreme hypertension, cerebrovascular accidents, pulmonary edema, atrial and ventricular arrhythmias, and headache.[37] MAOIs are contraindicated in patients with pheochromocytoma, congestive heart failure. and liver disease. Patients who are treated with MAOIs must be carefully selected for their ability to comply with dietary restrictions and refrain from taking any over-the-counter medications[38] (eg, pseudoephedrine, phenylephrine, and so on) without specific approval from the physician.

α_2-Adrenergic Antagonists

Mirtazapine is structurally unrelated to other antidepressants available in the United States. It appears to be an effective antidepressive agent, but published data are weak. Transient somnolence occurred in more than 50 percent of patients in US trials. Other common side effects include increased appetite, weight gain, dizziness, dry mouth, and constipation. There have been rare reports of agranulocytosis and neutropenia.[39]

Miscellaneous

Maprotiline, a tetracyclic antidepressant, blocks reuptake of norepinephrine at the neuronal membrane. Side effects (Table 4) include dizziness, drowsiness, seizures, orthostatic hypotension, electrocardiographic changes, tachycardia, dysrhythmias, blurred vision, constipation, paralytic ileus, hepatitis, urinary retention, and agranulocytosis. It is contraindicated in patients who have had recent myocardial infarction, concurrent use of MAOIs, or seizure disorder. The risk of seizures is increased when maprotiline is given with phenothiazines, when doses of benzodiazepines are rapidly tapered, and when recommended dosages of maprotiline are exceeded. Anticholinergic and sympathomimetic agents should be used with caution because of additive atropine-like effects.

Adjunct Therapy

Patients with incomplete response to a single antidepressant or who are unable to tolerate adequate doses because of side effects might benefit from combined treatment. An example would be using a low-dose TCA or trazodone along with an SSRI.[40] Triiodothyronine has also been reported to increase the efficacy of antidepressants in some patients regardless of preexisting thyroid status.[41] Low doses are used because of an increased risk of osteoporosis in patients on high doses of thyrox-

ine. Although more commonly prescribed for bipolar disorder, lithium carbonate is also used in unipolar depression, either alone or with another antidepressant medication.[42] Careful monitoring of lithium levels, electrolytes, and thyroid function is necessary.[43] Some potential side effects include drowsiness, difficulty concentrating, tremor, increased thirst, weight gain, diarrhea, and euthyroid goiter.[44,45] Indomethacin and some other nonsteroidal anti-inflammatory drugs have been reported to increase lithium levels.[46] Gastrointestinal illness with vomiting and diarrhea can increase lithium levels. Toxic effects of lithium are potentiated by calcium channel blockers, (eg, verapamil and diltiazem), diuretics, angiotensin-converting enzyme inhibitors, and anticonvulsants, such as carbamazepine and phenytoin.[47]

Table 6. Drugs That Increase and Decrease the Effects of Tricyclic Antidepressants (TCAs).

Increase TCA Levels	Decrease TCA Levels
Antihistamines (H_2)	Barbiturates
β-Blockers	Benzodiazepines
Diltiazem	Carbamazepine
Estrogens	Rifampin
Methylphenidate	
Oral contraceptives	
Phenothiazine	
Propafenone	
Propoxyphene	
Quinidine	
Selective serotonin reuptake inhibitors	
Verapamil	

General Prescribing Guidelines

A major cause of treatment failure in depression is patient noncompliance. One study reported that 60 percent of patients in primary care stopped treatment within 3 weeks.[48] Careful attention to patient education can improve compliance with the medication regimen. Because all of the antidepressants have side effects, patients must be carefully informed about what to expect. Some side effects, such as nausea or sedation, can be transient. If patients are so informed, they might be able to accept some discomfort knowing that they are likely to develop tolerance in 1 or 2 weeks. Other side effects can be life threatening, and it is important for patients to know which side effects must be reported to the physician.

Giving patients realistic expectations about the onset of action of the medication also helps encourage compliance. Physicians should emphasize that (1) the patient might not notice any improvement for several weeks, (2) these medications might require up to 8 weeks for a full therapeutic response,[49] and (3) antidepressants are effective only when taken continuously. Frequent office visits during early treatment help reduce the number of patients who stop their medication because they feel it is not helping when, in fact, they might not have reached therapeutic levels.

Duration of Antidepressant Therapy

Pharmacologic treatment should last for a minimum of 6 months after an initial episode. Most clinicians will continue treatment for at least 1 year for patients with a second episode. If the patient has responded, and symptoms are resolved, the decision can be made whether to taper the patient off of the drug or continue maintenance therapy. In a National Institute of Mental Health Collaborative Depression Study, one third of patients became ill again 1 year after recovery from an index episode of depression; almost one half became ill again by 2 years; and almost three quarters by 8 years.[50] Maintenance therapy may be continued indefinitely for patients with a history of frequent or multiple episodes of depression, major depression with preexisting dysthymia (double depression), onset of depression after the age of 60 years, long duration of individual episodes, severe index episode, poor symptom control during continuation therapy, and comorbid anxiety disorder or substance abuse. A strong family history of affective disorder also increases the risk of recurrence. Maintenance therapy with full doses of antidepressants is highly correlated with preventing recurrences for up to 5 years.[51]

When to Refer to a Psychiatrist

Although many depressed patients can be adequately cared for and monitored by the family physician, some patients clearly need to be under the care of a psychiatrist. Patients whose depression is severe or recurrent or who have suicidal tendencies, symptoms of bipolar disorder, or depression with psychotic features (delusions, hallucinations, loss of contact with reality) should be examined by a psychiatrist. Patients who fail to

Table 7. Effects of and Recommendations for Drugs That Interact With Tricyclic Antidepressants.

Drug	Effect	Recommendation
Antiarrhythmics	Class I: increased cardiotoxicity	Avoid or use lower doses
Androgens	CNS effects, paranoia	Avoid
Clonidine	Decreased antihypertensive effect	Increase clonidine or change medication
Disulfiram	Acute organic brain syndrome	Avoid
Guanethidine	Decreased antihypertensive effect	Increase dose or change medication
Guanfacine	Decreased antihypertensive effect	Increase dose or change medication
Hydantoins	Increased toxicity of hydantoin	Avoid
Levodopa	Sympathetic hyperactivity	Monitor symptoms
Lithium	Neurotoxicity, psychotic symptoms	Monitor symptoms
MAOIs	Hyperpyrexia, muscular rigidity Increased blood pressure, convulsions	Contraindicated
Sympathomimetics	Increased α-adrenergic effects of direct acting sympathomimetics	Monitor symptoms
	Decreased effects of mixed-acting sympathomimetics	
Sulfonylureas	Increased effect of sulfonylurea	Monitor for hypoglycemia

respond to treatment will also benefit from psychiatric evaluation. Alternative therapy, such as electroconvulsive shock therapy, can be safely administered by a competent psychiatrist. In convincing the patient to see a psychiatrist, it is helpful for the family physician to assure the patient of maintaining contact with both the patient and the psychiatrist. Continued contact avoids the patient feeling that he or she is being dumped and keeps the family physician aware of medication changes that can affect the patient's medical treatment.

Treating Depression in the Medically Ill Patient

Medically ill populations have an increased prevalence of major depression, reported from 20 to 40 percent. Many medical conditions can affect the metabolism of antidepressants, some antidepressants have negative effects on certain illnesses, and some other medications can increase or decrease the effects of TCAs (Tables 6 and 7). These factors should be considered when choosing a drug to treat depression in a patient with a concurrent medical illness.

Patients with liver disease might not metabolize antidepressants effectively. This possibility is most important clinically with TCAs, because toxicity occurs at blood levels only two to three times the therapeutic level. SSRIs, bupropion, and venlafaxine are also metabolized extensively in the liver, but they have a much wider therapeutic index.[52] Lower or less frequent doses are recommended for patients with cirrhosis.

Renal impairment lowers the clearance of fluoxetine, norfluoxetin (its active metabolite), bupropion, and venlafaxine. Starting with lower doses and gradually titrating to effect is the safest course for these patients.

Patients who have cardiovascular disease are vulnerable to drug effects and drug interactions. TCAs, even at therapeutic doses, have been shown to slow conduction through the AV node.[53] Effects appear to be more common in the elderly and in those with preexisting heart disease. Patients with bundle branch block are at increased risk for conduction disturbances caused by TCAs.[54] TCAs block the antihypertensive effects of clonidine, methyldopa, guanabenz, guanethidine, reserpine, and guanadrel, and can potentiate the effect of prazosin. In patients with congestive heart failure, TCAs can cause severe orthostatic hypotension as a result of α_1-adrenergic blockade.[55]

Trazodone has been reported to be arrhythmogenic in patients with preexisting cardiac irritability. There are also some case reports of arrhythmias or syncope in patients with cardiac disease who have been taking fluoxetine. Bupropion appears to be the safest antidepressant for patients with preexisting heart disease.[56,57]

In depressed patients with a history of cerebrovascular accidents, the SSRIs are generally the drugs of choice because they have fewer anticholinergic effects and sedation than TCAs. If a TCA is prescribed, a secondary amine, such as

nortriptyline is preferred, as it will cause less sedation and fewer anticholinergic effects.[58]

Diabetic patients can have increased sensitivity to insulin and oral hypoglycemic medications when their depression is treated with MAOIs at low doses and increased insulin resistance when treated at higher doses. Tricyclic antidepressants can provide some relief from the pain of diabetic neuropathy, although other classes of antidepressants do not.[59] SSRIs can alter glycemic control. Patients should be carefully monitored for hypoglycemia or hyperglycemia when antidepressant therapy is started.

Amoxapine should not be prescribed for patients with Parkinson disease; it has a metabolite that has potent dopamine receptor blocking activity. Selegiline, which is frequently prescribed for Parkinson patients, is a selective MAO-B inhibitor. Patients taking selegiline should not also take SSRIs or TCAs because of the potential for serious interactions.[60] For patients not taking selegiline, effective agents include imipramine, nortriptyline, desipramine, and bupropion. Bupropion is weakly dopaminergic and might also beneficially affect the movement disorder. Amitriptyline is useful for patients who have sleeping difficulties and excessive salivation.[61]

Depressed cancer patients can be helped by TCAs, which can increase appetite in anorectic patients, but susceptibility to side effects in this population limits usefulness. Nausea and weight loss, which are common side effects of the SSRIs and bupropion, are undesirable in this population. Venlafaxine or nefazodone might be reasonable alternatives. MAOIs are contraindicated with meperidine and must be prescribed cautiously with other pain medications.

Some demented patients are also depressed, and appropriate treatment will improve their quality of life. Prevalence of depression has been reported as high as 20 to 30 percent among dementia patients. There is no unique symptom or profile to differentiate dementia from masked depression, as both have similar features, particularly in the elderly. (Dementia of depression is cognitive impairments associated with depression that resolve with treatment of the depression.[62]) Formal psychometric testing might be helpful. True dementia will not improve with the treatment of depression, but the depressive symptoms will.

Patients who are agitated might benefit from more sedating antidepressants, such as trazodone or nefazodone. In some patients sedation will further reduce mentation. MAOIs can be useful in patients who are institutionalized to control their diets and medications. Bupropion and venlafaxine have less-adverse effects on cognition but must be prescribed with caution because of the potential for agitation.[63]

Treating depression secondary to alcoholism can reduce the risk of relapse in patients with major depression that is diagnosed after 1 week or longer of abstinence.[64] Antidepressant treatment does not reduce relapse rates in patients who are not depressed.

Patients with narrow-angle glaucoma should not be treated with drugs that have anticholinergic effects, such as tricyclic antidepressants.

Obese patients might respond better to bupropion, an SSRI, or venlafaxine, as these drugs do not cause the weight gain that is associated with other antidepressants.

Treating Depression in the Elderly

Depression is the most common emotional disorder in the patients older than 65 years and is associated with a higher risk of death from suicide than for any other age group.[65] Elderly patients must be monitored more carefully because their altered drug metabolism can cause therapeutic failure from undertreatment or toxicity from overtreatment. The SSRIs are well tolerated in this group, and patients are less likely to stop taking them because of untoward side effects.[66] Nortriptyline also provides effective treatment and has fewer side effects in this age group than other tricyclic medications.[67]

Elderly patients should be started at lower doses than younger adults. The usefulness of TCAs is limited by anticholinergic effects and sedation. Among the TCAs, desipramine is less anticholinergic, but can be too activating for some patients. Orthostatic hypotension increases the risk of falls and hip fractures.[68]

- Trazodone, which can cause orthostatic hypotension and worsen cardiac arrhythmias, is sometimes used to promote sleep by administering it in low doses at bedtime along with a more activating drug during the day.[69] Most elderly patients cannot tolerate doses of trazodone large enough to treat depression.

Pediatric Patients

Childhood depression has been treated with intensive psychotherapy.[70] In a meta-analysis of antidepressant medication outcome studies that involved children and adolescents, open-label studies showed efficacy, but blinded studies showed no difference from placebo.[71] Heterocyclic antidepressants are metabolized more quickly in adolescents than in adults and more quickly still in younger children. Plasma levels should be monitored. Rapid hepatic metabolism of serotonergic parent compounds, such as imipramine and amitriptyline, results in noradrenergic active metabolites, shifting the ratio of noradrenergic to serotonergic activity higher than that in adults. This shift is important because the noradrenergic system does not fully develop both anatomically and functionally until early adulthood.[72]

Because there have been reports of sudden cardiac death, a baseline electrocardiogram and periodic electrocardiographic monitoring are recommended if these drugs are used in children. Prolongation of the PR interval or increased blood pressure are indications to reduce the dose or discontinue the medication.[72]

Generally, safety and effectiveness of other antidepressants have not been established in children. For the child with severe depression, a psychiatrist should be consulted.

Pregnancy and Lactation

Lithium is reported to be teratogenic in the first trimester.[73] SSRIs, maprotiline, and bupropion are rated pregnancy category B, which means that while there were no harmful effects reported in animal studies, there are no reliable data on safety in humans during pregnancy. Recently published data showed that children with three or more minor structural anomalies were more commonly born to women exposed to fluoxetine during pregnancy, and women exposed to fluoxetine during the third trimester were more likely to have premature deliveries and low-birth-weight infants.[74] Amoxapine, desipramine, imipramine, protriptyline, the MAOIs, nefazodone, trazodone, and venlafaxine are category C medications, and amitriptyline and nortriptyline are category D. These drugs should be used in pregnancy only when the benefit clearly outweighs the risk, as when the life of the mother and fetus are in danger. Inpatient treatment for severe depression might be preferable to antidepressant therapy, and electroconvulsive therapy has been used safely during pregnancy.[75,76]

A recent meta-analysis of studies evaluating serum levels in nursing infants whose mothers were taking antidepressants reported adverse effects on infants whose mothers were treated with doxepin and fluoxetine. Of studied antidepressants available in the United States, amitriptyline, nortriptyline, desipramine, clomipramine, and sertraline had no reported adverse effects on nursing infants.[77]

Concurrent Psychiatric Diagnoses

If there is more than one psychiatric diagnosis, the choice of antidepressant must be carefully considered. History of a manic or hypomanic episode indicates bipolar disorder, and antidepressants must be used with caution because of the danger of inducing a manic state. Lithium and anticonvulsants, such as carbamazepine and valproate, are sometimes effective alone or with an antidepressant.

SSRIs and tricyclic antidepressants are effective in patients with major depressive disorder and concurrent dysthymia, sometimes referred to as double depression.[78] Major depression frequently coexists with panic disorder.[79] Tricyclic antidepressants are highly effective in blocking the autonomic expression of panic, thus facilitating a comprehensive rehabilitation program. Bupropion can worsen symptoms of panic disorder.[80] In patients with concurrent anxiety, medications with shorter half-lives should be prescribed at a lower dose and increased gradually; drugs with potent anticholinergic side effects should be avoided.[81] Concurrent substance abuse, posttraumatic stress disorder, and dissociative disorders are beyond the scope of this review. Psychotic symptoms, such as hallucinations, can occur with depression as well as with a coexisting psychosis and are indications for formal psychiatric evaluation.

Conclusion

Of the many antidepressants available, the selective serotonin reuptake inhibitors have become preferred for many patients because of their safety and lower incidence of serious side effects. Drug interactions must be taken into account, and concurrent medical illnesses can affect the choice of antidepressants. Patient education re-

garding side effects, duration of treatment, and time to onset of therapeutic effect is essential to encourage compliance. The psychotic, suicidal, or bipolar patient or the patient unresponsive to a reasonable trial of antidepressant therapy should be seen by a psychiatrist.

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