New Antidepressants and the Treatment of Depression

Barry H. Guze, MD, and Michael Gitlin, MD
Los Angeles, California

Depression is a common and significant health problem associated with impairment in a patient's ability to function. The development of new antidepressant medications represents progress in its treatment. These new agents work through the selective blockade of the reuptake of serotonin into the presynaptic neuron, thereby increasing the availability of this neurotransmitter at the synaptic cleft and enhancing its effectiveness. While no more effective than traditional tricyclic antidepressant drugs, the new agents are generally safer than traditional medications used to treat depression: they are well tolerated and, in case of overdose, less harmful than tricyclic antidepressants.

Key words. Serotonin antagonists; antidepressants; depression; antidepressive agents, tricyclic.
(*J Fam Pract 1994; 38:49-57*)

Depression is a common condition.[1] Among the noninstitutionalized elderly, the prevalence of clinically significant depression is about 15%.[2] With a lifetime prevalence of 6% and associated risks such as suicide, major depression is an important public health concern in the United States.[3] In 1979 and still in 1989, suicide was the fourth leading cause of death for white Americans.[4]

The economic impact of depression in the United States has been estimated at more than $16 billion, only $2.1 billion of which is spent on diagnosis and treatment.[5,6] The balance is associated with lost productivity. Major depression produces impairment in functioning close in magnitude to that of chronic heart disease[7] and exceeding that of many other chronic diseases. The risk of disability in minor depression is 1½ times that of asymptomatic individuals; for major depression, it is 4½ times.[8]

The chronic nature of depression is exemplified by the high rate of recurrence among patients experiencing an initial episode.[9-11] Approximately 50% of patients who recover from an initial bout with depression will have at least one subsequent episode during the following 2 years.[11] The factors associated with a heightened probability of relapse include the severity of the initial episode, the number of prior episodes, the response to prior treatment, and a history of chronic depression.[10] Other important factors include comorbid conditions, such as chronic medical conditions, and the degree of psychosocial perturbation. Because recurrence is so common, early and aggressive treatment of depression has been recommended.[12]

Depression is usually treated by primary care physicians. Major depression has been reported to be more common than hypertension in primary care practice,[13] and the presence of a psychiatric diagnosis is found in 11% to 36% of patients in general practice.[14] The recognition of major psychiatric illness is poor, however, with estimated rates for failure to detect depression ranging from 45% to 90%.[15,16] In a study of nursing home patients, only 12.5% of major depression cases were recognized and even fewer treated by staff physicians. An accurate differential diagnosis of mood disorder is the key to appropriate treatment. Diagnosis of a major depressive episode is appropriate when at least five of the symptoms listed in Table 1 are present nearly every day for at least 2 weeks.[17] One of these symptoms must be "depressed mood" or "loss of interest or pleasure in most or all activities."

Not all physicians are taking advantage of new developments in effective treatments to decrease the morbidity and mortality associated with depression.[18] Con-

Submitted, revised, September 8, 1993.

From the Department of Psychiatry and Biobehavioral Sciences, School of Medicine, and the Neuropsychiatric Institute and Hospital, University of California, Los Angeles. Requests for reprints should be addressed to Barry H. Guze, MD, UCLA NPI, 760 Westwood Plaza, Los Angeles, CA 90024.

 ISSN 0094-3509

Table 1. Symptoms of Depression

Depressed mood most of the day
Loss of interest or pleasure in most or all activities
Significant change in weight or appetite
Insomnia or hypersomnia
Psychomotor retardation or agitation
Fatigue or loss of energy
Feelings of worthlessness or of excessive or inappropriate guilt
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death, recurrent suicidal ideation, or suicide attempt

NOTE: *Diagnosis of a major depressive episode is appropriate when a minimum of five symptoms, one of which is "depressed mood" or "loss of interest or pleasure in most or all activities," are present nearly every day for at least 2 weeks.*

scientious long-term care, coupled with attention to patient compliance with treatment, can substantially reduce the suicide rate among patients with mood disorders. When proper recognition and pharmacologic treatment of depression occurs, suicide rates can be lowered,[19,20] as exemplified by a two-session educational program on treating depression that was provided to general practitioners on the Swedish island of Gotland. This program reduced the suicide rate by 71% as compared with the general rate in Sweden,[21] suggesting that increased recognition of depression and knowledge regarding its treatment can have an impact on mortality.

Depressive disorders can be divided into five categories: major depression, dysthymia, bipolar-disorder depression, cyclothymia, and depressive disorder not otherwise specified.[17] Major depression itself can be further subtyped into groups with and without psychotic features (delusions and hallucinations). Psychosis is present in 10% to 25% of patients with major depression.[22] The presence of psychotic features often results in a different approach to treatment.[23] Electroconvulsive therapy is thought by many to be the most effective treatment for this form of depression. The other approach is the combination of a tricyclic antidepressant and a neuroleptic.[23] In most cases of depression, treatment with antidepressant medication alone is inadequate.

Choice of an Antidepressant

Pharmacotherapy is the most effective treatment for moderate to severe nonpsychotic depression,[24] with traditional antidepressants being effective in approximately 60% to 85% of patients.[25] Current treatment options include traditional tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), tetracyclic antidepressants (eg, maprotiline), and selective serotonin reuptake inhibiting (SSRI) antidepressants (Table 2). Tetracyclic compounds predominantly affect norepinephrine neurotransmission, are pharmacologically similar to the tricyclic

Table 2. Dosage and Administration of Three Selective Serotonin Reuptake Inhibitors

Medication	Usual Daily Dosage, mg	Range, mg	Comments
Paroxetine	20	10–50	No active metabolites
Sertraline	50	50–200	No active metabolites
Fluoxetine	20	5–80	Active metabolite with long half-life

antidepressants, and offer the same side-effect profile and efficacy as tricyclic antidepressants.[26]

Selective serotonin reuptake inhibitors, the new antidepressant agents that recently have become available in the United States, are no more effective than traditional agents, but their side-effect profiles often present important clinical advantages, such as lower incidence of side effects compared with standard tricyclic and tetracyclic antidepressant drugs[25] (Table 3). The mildness of their side effects makes them particularly well suited for treating moderately depressed outpatients or the elderly.[27] The SSRIs also are used to treat conditions other than depression, including bulimia nervosa,[28] personality disorders,[29] and obsessive-compulsive disorder.[30] Treatment of these conditions requires higher dosages than the dosages to treat depression.

It has been estimated that 75% to 80% of patients taking tricyclic antidepressants receive subtherapeutic doses because of the intolerable side effects associated with higher dosages.[31] Thus, side effects may limit the clinical effectiveness of traditional antidepressant medications. In addition to subtherapeutic dosing, side effects associated with tricyclic antidepressants often result in long titration trials, premature discontinuation of therapy, or lack of patient compliance, along with overdose fatalities.[32] In clinical trials, twice as many patients have discontinued tricyclic antidepressants as have discontinued fluoxetine.[32]

Traditional tricyclic antidepressant side effects in-

Table 3. Common Side Effects of Selective Serotonin Reuptake Inhibitors (SSRIs)

Nausea
Somnolence
Weakness
Dizziness
Insomnia
Sexual dysfunction
Sweating
Tremor
Decreased appetite
Nervousness

NOTE: *SSRIs may interact with MAOIs to produce serotonin syndrome.*

clude orthostatic hypotension, alterations in cardiac conduction, overdose fatality, dry mouth, constipation, blurred vision, urinary hesitancy, and memory impairment,[26] none of which are associated with SSRIs.[25] Typical side effects of the SSRIs include gastrointestinal upset, such as nausea and diarrhea; restlessness or akathisia; insomnia; and headache (Table 3). Generally, these agents do not adversely interact with commonly abused drugs or alcohol. When used alone, the SSRIs usually are not fatal in overdose[32] and are not known to have significant effects on cardiac function.

Abrupt discontinuation of the tricyclic antidepressants has been associated with a withdrawal syndrome,[33] which occurs in 20% to 60% of patients and consists of sleep disturbances (vivid dreams, insomnia), anxiety or agitation, movement disorders (akathisia and parkinsonism), and behavioral disturbances (hypomania).[34] The SSRIs are not associated with a withdrawal problem,[32] nor are they reported to cause depression recurrence on abrupt discontinuation as sometimes occurs with other antidepressants.[35]

With the introduction of SSRIs, the choice of an antidepressant has become more difficult. It is unclear whether these new medications should replace tricyclic antidepressants as first-line treatment of the typical patient with depression. It can be argued that the SSRIs are effective and usually tolerated better than tricyclic antidepressants in the treatment of mild or moderate depression.[36] More clinicians are beginning to use SSRIs in severe depression where data suggest that they are as effective as tricyclic antidepressants.[37,38] The SSRIs are gaining favor over tricyclic antidepressants as primary or "first line" agents in treating mild to moderate depression because of their safety, efficacy, and simple dosing regimen.[39]

Serotonin and Mood

Multiple observations suggest that serotonin, one of the most abundant neurotransmitters, plays an important role in the regulation of mood and a key role in the treatment of depression. Data suggest that depression is associated with reduced serotonin function.[40] Studies of cerebrospinal fluid, whole blood, and plasma have shown that serotonin levels[41–43] as well as 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, are reduced in depressed patients.[44,45] Depression also is associated with altered serotonin receptor function in platelets and in postmortem brain samples from depressed patients.[44–48]

Selective Serotonin Reuptake Inhibitors

Paroxetine, sertraline, and fluoxetine are members of the SSRI group that are currently marketed in the United States. Fluvoxamine and citralopram are not currently available for clinical use, although approval for marketing of fluvoxamine is expected soon. The SSRIs act by strongly inhibiting the reuptake of serotonin into the presynaptic neuron.[49,50] Whereas traditional tricyclic antidepressants, particularly clomipramine, inhibit the reuptake of serotonin following its release from presynaptic terminals, these medications or their active metabolites also inhibit uptake of other neurotransmitters, such as norepinephrine.[25]

During normal neurotransmission, serotonin is stored in presynaptic vesicles until it is released into the synaptic cleft.[25] Serotonin then activates postsynaptic receptors, producing postsynaptic neuronal stimulation. Serotonin then is inactivated by several mechanisms, including its removal from the synaptic cleft by the reuptake pump on the presynaptic neuron. Within the presynaptic neuron, it undergoes either repackaging in a vesicle or metabolism by mitochondria containing monoamine oxidase. The mechanism of action for the SSRIs is the blocking of the uptake pump action on the presynaptic neuron.[25] This increases the amount of serotonin in the synaptic cleft and at the postsynaptic serotonin receptor site, resulting in greater postsynaptic serotonin stimulation.[51]

Depression may be associated with reduced availability of serotonin in the synapse. In vivo, the SSRIs also downregulate postsynaptic norepinephrine receptors and affect adenylate cyclase–mediated reactions coupled with postsynaptic receptors.[25] It is possible that the property of serotonin reuptake inhibition may be of little clinical significance. In contrast to the SSRIs, tricyclic antidepressants exert nonspecific effects at reuptake and receptor sites for many neurotransmitter systems.[50,52]

The SSRIs are well absorbed following oral administration and subsequently undergo significant first-pass extraction in the liver.[53] These agents are cleared predominantly by hepatic metabolism, with fluoxetine and sertraline producing active metabolites. The pharmacology of these drugs is characterized by marked interindividual variability.[53]

Since there is no evidence that any one SSRI is more effective than any other in the treatment of depression,[25] clinicians often choose between different SSRIs primarily on the basis of varying side effects; but there are meaningful distinctions among the SSRIs that also should be taken into consideration. For example, fluoxetine appears to be the most activating of the agents.[27] The half-life of

Table 4. Pharmacokinetic Properties of the Selective Serotonin Reuptake Inhibitors

Property	Paroxetine	Sertraline	Fluoxetine
Active metabolite	No	Yes	Yes
Half-life of parent compound (days)	1	1	2–3
Half-life of active metabolite (days)	None	2–4	7–9

various antidepressants and of their active metabolites, when present, determines time to steady state and the washout period (Table 4), which is particularly significant when switching to other antidepressant agents or waiting for the resolution of adverse drug effects. The advantages of a long half-life are that it permits a patient to be treated with doses given every few days and may control brief episodes of noncompliance.

The combination of an SSRI with an MAOI should be avoided because concurrent administration may precipitate the serotonin syndrome, consisting of hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that may progress to delirium, coma, and death resulting from cardiovascular collapse.[54–57] Other features of the serotonin syndrome may include hyperarousal, exaggerated deep tendon reflexes, exaggerated startle response, hypertension, mild manic symptoms, diarrhea, abdominal cramping, and tremor. To avoid the development of serotonin syndrome, the patient should discontinue an SSRI at least 2 weeks before the administration of an MAOI, although a longer period may be required for fluoxetine because of the long half-life of its active metabolite. A washout period does not appear necessary when other SSRIs are administered subsequently. For example, it is safe to stop fluoxetine administration and begin paroxetine the following day.[58]

Because sertraline is tightly bound to plasma proteins, it may interact with other medications that are also highly protein-bound and produce adverse effects.[56,57] The effect of using sertraline in combination with other central nervous system active medications has not been systematically evaluated. For these reasons, caution is advisable when coadministering these medications.

There is concern regarding the association between some SSRIs, such as fluoxetine, and an increased risk of suicide.[59] Pooled data from clinical trials suggest that fluoxetine does not increase the suicide risk.[60] The US Food and Drug Administration's Psychopharmacological Drugs Advisory Committee reviewed the issue and, based in part on a reanalysis of all the controlled trials involving the use of fluoxetine, concluded that there was no causal link between the use of antidepressant drugs and suicide or violent behavior.[61] There is no evidence that fluoxetine increases suicidal ideation.[60]

Paroxetine

PHARMACOLOGICAL PROPERTIES

Paroxetine is well absorbed from the gastrointestinal tract and is unaffected by antacids or food.[62] Steady-state plasma concentrations are reached within 4 to 14 days.[53,62] It has a plasma half-life of approximately 24 hours.[62] Because paroxetine has no active metabolites, it has a shorter washout period than the other SSRIs, which may be advantageous when changing pharmacologic agents.[53]

Paroxetine is oxidated, methylated, and then conjugated in the liver. Although the drug has no active metabolites, coadministered medications that induce or inhibit hepatic metabolic enzymes may affect blood levels of paroxetine. Because increases in bleeding time were observed in volunteers who received paroxetine and warfarin simultaneously, caution should be exercised in patients receiving paroxetine and oral anticoagulants. Paroxetine does not potentiate the effects of alcohol, barbiturates, antipsychotics, or benzodiazepines.[62]

EFFICACY

Data based on the treatment experience of over 4000 depressed patients suggest that paroxetine is as effective as other antidepressant medications, including fluoxetine,[64] and superior to placebo in the treatment of major depression.[55,63,64] Paroxetine produces a significant improvement in depression-induced lethargy, usually within the first 1 to 2 weeks.[63] Symptoms of lethargy include fatigue, decreased motor activity, difficulty concentrating, and lack of interest in work and activities. Despite side effects that include stimulation, paroxetine reduces associated symptoms of anxiety in depression with minimal agitation.[63] In a study of 2963 patients treated with paroxetine, the drug did not cause emergent anxiety any more frequently than placebo.[65] Paroxetine is an effective maintenance treatment for preventing relapse in depression.[66]

ONSET OF ACTION

Onset of significant clinical antidepressant effects may not be seen for the first 2 or 3 weeks of treatment, as is true with all antidepressants,[63] but paroxetine exhibits a more rapid initial therapeutic onset than other SSRIs or tricyclic antidepressants.[64]

SIDE EFFECTS

The most common side effects of paroxetine are those found in other SSRIs, including dry mouth, nausea, headache, somnolence, insomnia, diarrhea, constipation, and tremor,[55] all of which seem to diminish with time. Paroxetine may be less stimulating or activating than fluoxetine to the extent of inducing sedation in some patients. Paroxetine has not been associated with significant changes in weight, cardiac function, or electrocardiogram[67–69] and does not inhibit the reuptake of other neurotransmitters except for serotonin.[62] Consequently, it does not cause many of the side effects associated with tricyclic antidepressant medication.[70]

DOSAGE AND ADMINISTRATION

The usual initial dose of paroxetine, which for most patients is the usual effective dose, is 20 mg per day.[71] The upper limit of the effective range with no clinically significant increase in side effects is 50 mg per day. Since the elimination half-life of paroxetine is increased in patients with renal impairment,[72] a lower dose is recommended for these patients (creatinine clearance <30 mL per minute). The initial dose should be reduced to 10 mg per day and doses increased as clinically indicated.

CONTRAINDICATIONS

As noted above, recent or concurrent administration of MAOIs may result in serotonin syndrome.

Sertraline

PHARMACOLOGIC PROPERTIES

Sertraline is a selective serotonin reuptake-inhibitor[51] that is well absorbed (90%) after oral administration, with peak serum levels occurring 6 to 8 hours after administration.[53,56,57] Peak plasma levels are 30% higher when the drug is administered with food, which probably results from substances in food competing with sertraline for metabolism in the liver. Therefore, the drug should be administered with food. Serum half-life is approximately 24 hours.[53,56,57] The pharmacokinetic profile of sertraline permits once-a-day dosing.[73] Metabolism occurs in the liver; no active metabolites are formed.[51] Sertraline does not induce its own hepatic metabolism. The metabolism of sertraline is linear: doubling the dose doubles the serum level. Sertraline does not potentiate alcohol or other recreational drugs.

EFFICACY

Sertraline has demonstrated greater effectiveness than placebo in doses ranging from 50 mg to 200 mg per day.[74] The results of a multicenter, parallel, placebo-controlled study of outpatients with major depression randomized to receive sertraline, amitriptyline, and placebo demonstrated that sertraline was as effective as amitriptyline, and both were more effective than placebo.[75] However, because the majority of clinical studies to date have been performed on mild to moderately depressed outpatients, the efficacy of sertraline has not been established for severe depression.[25]

In addition to established efficacy in the acute treatment of mild to moderate depression, sertraline is also useful in the prevention of future depressive episodes.[38] This effectiveness has been established in continuation therapy trials of sertraline vs placebo for up to 44 weeks' duration, during which the relapse rate with sertraline was considerably lower than with placebo. Sertraline also is as effective as amitriptyline in the treatment of elderly depressed patients where comparable efficacy was observed between sertraline and amitriptyline in patients with moderate or severe depression.[76]

ONSET OF ACTION

The onset of action is similar to that of tricyclic antidepressants: early improvement is seen in 3 weeks, and maximum drug-placebo difference occurs in 6 weeks.

SIDE EFFECTS

Patients receiving therapeutic doses of sertraline are unlikely to experience impairment of psychomotor performance while engaged in daytime activities.[77] Side effects that occur in more than 5% of patients receiving sertraline include nausea, diarrhea or loose stools, dyspepsia, tremor, dizziness, insomnia, somnolence, increased sweating, dry mouth, and male sexual dysfunction (primarily ejaculatory delay).[56,57] In most cases, side effects are mild and well tolerated by the patient, but in some cases, side effects are sufficient to justify discontinuation of the medication. During the acute treatment phase of one study, 4% of patients discontinued sertraline because of side effects. During a 44-week continuation study, in which the mean maintenance dose of sertraline was 70 mg per day, the incidence of side effects was similar to that of placebo.[38]

Sertraline has few cardiovascular side effects in patients without heart disease,[78] but there is limited experience with patients who have a recent history of myocardial infarction or unstable heart disease. Little is known about the dangers associated with overdose, but no serious problems have been reported. In known cases of overdose, recovery has occurred in 24 to 48 hours, without seizures or significant cardiovascular dysfunc-

tion. There have been no reports that sertraline increases a patient's risk for suicide or violence.[11]

DOSAGE AND ADMINISTRATION

Sertraline is administered in a single daily dose of between 50 mg and 200 mg. The usual initial dose is 50 mg per day,[56] which is effective for most patients (60% to 70% of patients respond to 50 mg per day).[57] Patients not responsive to the 50-mg dose may benefit from increases up to a maximum of 200 mg per day. Dosages rarely should exceed 200 mg per day because of notably increased side effects associated with greater dosages.

CONTRAINDICATIONS

As noted above, sertraline may interact with MAOIs.

Fluoxetine

PHARMACOLOGIC PROPERTIES

The clinical pharmacology of fluoxetine is well understood.[79] Fluoxetine is a selective inhibitor of serotonin reuptake. It has little effect on other neurotransmitters. Fluoxetine is well absorbed after oral administration, with peak levels occurring 6 to 8 hours after administration.[56,57] Fluoxetine itself has a half-life of 2 to 3 days, whereas its active metabolite, norfluoxetine, has a half-life of 7 to 9 days,[57] which may protect against sporadic noncompliance. The drug is 94% protein-bound. Fluoxetine affects the cytochrome P450 system and may result in alterations of the serum concentrations of other medications, such as neuroleptic and tricyclic antidepressants.[80,81] Elevated levels of haloperidol,[82] carbamazepine,[83,84] and valproate[85] have occurred during coadministration with fluoxetine.

EFFICACY

In nonpsychotic depressions, fluoxetine is as effective as tricyclic medications[87–89] and may be particularly effective in patients with chronic, treatment-refractory depression.[86,87] Because of the few, mild side effects of fluoxetine, it has a higher efficacy index (defined as therapeutic-effect score/side-effect score) than traditional tricyclic antidepressants when compared in clinical trials.[88] Fluoxetine also is effective in long-term prophylaxis,[89] and its benign side-effect profile results in a low dropout rate during maintenance treatment.[89]

ONSET OF ACTION

Like other antidepressants, fluoxetine requires 3 to 6 weeks for significant symptom resolution to occur.[90,91]

SIDE EFFECTS

Side effects associated with fluoxetine include nausea, nervousness, anxiety, and insomnia. In approximately 15% of patients, side effects are severe enough to cause discontinuation of medication.[92] For the majority, however, side effects are mild and often time-limited. Fluoxetine may produce a subjective sense of inner restlessness that resembles neuroleptic-induced akathisia, a possible result of serotonin-induced nigrostriatal dopamine reduction.[5] On rare occasions, akathisia has been linked to dysphoria in some patients that may have precipitated suicide attempts,[93] but there are no data to confirm an increased risk for suicide or violence in patients being treated with fluoxetine.[60]

DOSAGE AND ADMINISTRATION

The initial and maintenance dosage of fluoxetine is 20 mg per day, which is adequate for most patients, but dosages may range from 5 to 80 mg per day.[56,57,94] Dosages ranging from 60 to 80 mg per day are commonly used to treat refractory patients.[94,95] Increases in dosage beyond 20 mg per day usually are effected in 20-mg increments over a 2-week or longer period. There have been recent reports of patients treated with dosages ranging from 100 mg to 320 mg of fluoxetine per day.[96] Such high doses usually are reserved for patients resistant to prior treatment manifested as partial to no response to lower dosages. As dosage increases, fluoxetine's usual side effects tend to become more pronounced,[97] and additional side effects may appear: headache, insomnia, gas, sore throat, transient hypomania or mania, grand mal seizures, and mild laboratory abnormalities on liver-function testing.

There is disagreement regarding the need for increases in fluoxetine dosage for treatment-refractory patients. Some maintain that additional time, rather than further increases in dosage, is required for the 20-mg dose to be effective.[87] There also are case reports of patients being treated successfully with 20 mg every other day, but clinical indications for this treatment are not fully known.[98]

CONTRAINDICATIONS

Since fluoxetine is metabolized in the liver, it should be used cautiously in patients with impaired hepatic function.[21] For these, a lower dose or less frequent dosing is advisable because hepatic disease extends the elimination half-life from approximately 2 or 3 days to 7 days.[21] No absolute contraindications to the use of fluoxetine are known. As with other SSRIs, fluoxetine used with MAOIs may result in serotonin syndrome, which sug-

gests that 5 weeks should elapse after the administration of fluoxetine before starting an MAOI. Five weeks is recommended because of the long half-life of the fluoxetine's active metabolite.

DRUG INTERACTIONS

Because fluoxetine inhibits hepatic microsomal enzymes, it may impair the clearance and increase the plasma concentration of coadministered medications, such as tricyclic antidepressants, carbamazepine, valproic acid, diazepam, alprazolam, and chloral hydrate.[27,50,99–101] Norfluoxetine may contribute to the effect of fluoxetine in inhibiting metabolism, as the higher the levels of both compounds, the greater the degree of inhibited metabolism.[102]

Conclusions

Optimal treatment of depression is predicated on several factors, including adequate differential diagnosis and appropriate treatment. Optimal prescribing practices may be inhibited by myths about depression.[103] For example, although sadness is commonly associated with depression, it is not an essential component of the disease. Current diagnostic criteria more accurately specify a dysphoric mood or loss of interest or pleasure.[17] The decision to treat should be based on severity of symptoms, not on whether the depressive state is justified. Antidepressants also may be appropriate for the chronically depressed, those who have been continuously depressed for more than 2 years.

Because depression is often chronic, maintenance treatment is an essential consideration.[104] Generally, clinicians continue antidepressant medications for at least 6 months after the resolution of symptoms in an uncomplicated episode of depression. Maintenance treatment of 2 years' duration usually is initiated in patients who have had more than one severe episode of depression or who have had several episodes in the previous 5 years.[105]

New antidepressants, consisting principally of the serotonin reuptake blockers, represent an additional therapeutic option for physicians. In general, these drugs are well tolerated, have few of the side effects associated with traditional antidepressant medications, and are as effective as traditional tricyclic antidepressants for nonpsychotic depression. Unfortunately, many of these agents are more expensive than their prececessors, which may be a significant disadvantage in some populations.

Acknowledgments

This report was supported, in part, by the National Institute of Mental Health (K07 MH00912) (BHG).

References

1. Regier DA, Myers JK, Kramer M, et al. The NIMH epidemiologic catchment area population characteristics. Arch Gen Psychiatry 1984; 41:934–41.
2. Cohen GD. Prevalence of psychiatric problems in older adults. Psychiat Ann 1990; 20:433–8.
3. Reigier DA, Boyd JH, Burke JD, et al. One month prevalence of mental disorders in the United States. Arch Gen Psychiatry 1988; 46:977–86.
4. Centers for Disease Control. Trends in years of potential life lost before age 65 among whites and blacks—1979–1989. JAMA 1992; 268:3423.
5. Regier DA, Hirschfeld RMA, Goodwin FK. The NIMH Depression Awareness, Recognition and Treatment Program: structure, aims and scientific basis. Am J Psychiatry 1988; 145:1351–7.
6. Stoudemire A, Frank R, Hedemark N. The economic burden of depression. Gen Hosp Psychiatry 1986; 8:387–94.
7. Wells KB, Stewart A, Hayes RD, et al. The functioning and well-being of depressed patients: results from the medical outcomes study. JAMA 1989; 262:914–9.
8. Broadhead WE, Blazer DG, George LK, et al. Depression, disability days and days lost from work in a prospective epidemiologic survey. JAMA 1990; 264:2524–8.
9. Hirschfeld RMA, Goodwin FK. Mood disorders. In: Talbot JA, Hales RE, Yudofsky SC, eds. Textbook of psychiatry. Washington, DC: American Psychiatric Press, Inc, 1988:403–41.
10. Thase ME. Relapse and recurrence in unipolar major depression: short-term and long-term approaches. J Clin Psychiatry 1990; 51(suppl):51–7.
11. NIMH/NIH Consensus Development Panel. Mood disorders: pharmacologic prevention of recurrences. Am J Psychiatry 1985; 142:469–76.
12. Angst J, Baastrup P, Grof P, et al. The course of monopolar depression and bipolar psychoses. Psychiatr Neurol Neurosurg 1973; 76:489–500.
13. Katon W. The epidemiology of depression in medical care. Int J Psychiatry Med 1987; 17:93–112.
14. Barrett JE, Barrett JA, Oxman TE, et al. The prevalence of psychiatric disorders in a primary care practice. Arch Gen Psychiatry 1988; 45:1100–6.
15. Schulberg HC, Burns BJ. Mental disorders in primary care: epidemiologic, diagnostic and treatment research directions. Gen Hosp Psychiatry 1988; 10:79–87.
16. Ormel J, van den Brink W, Koeter MWJ, et al. Recognition, management and outcome of psychological disorders in primary care: a naturalistic follow-up study. Psychol Med 1990; 20:909–23.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, ed 3, rev. Washington, DC, American Psychiatric Press, Inc, 1987.
18. Depression and suicide: are they preventable? [editorial]. Lancet 1992; 340:700–1.
19. Rihmer Z, Barsi J, Veg K, et al. Suicide rates in Hungary correlate negatively with reported rates of depression. J Affect Disord 1990; 20:87–91.
20. Isacsson G, Boethius G, Bergman U. Low level of antidepressant prescription for people who later commit suicide: 15 years of experience from a population-based drug database in Sweden. Acta Psychiatr Scand 1992; 85:444–8.
21. Rutz W, Knorring L, Walinder J. Frequency of suicide on Gotland after systematic postgraduate education of general practitioners. Acta Psychiatr Scand 1989; 80:151–4.
22. Coryell W, Pfohl B. The clinical and neuroendocrine features of psychotic depression. J Nerv Ment Dis 1984; 72:521–8.
23. Spiker DG, Weiss JC, Dealy RS. The pharmacologic treatment of delusional depression. Am J Psychiatry 1985; 142:430–6.
24. Elkin I, Shea MT, Watkins JT. National Institute of Mental Health Treatment of Depression Collaborative Research Pro-

gram: general effectiveness of treatments. Arch Gen Psychiatry 1989; 46:971–83.
25. Baldessarini RJ. Current status of antidepressants: clinical pharmacology and therapy. J Clin Psychiatry 1989; 50:117–26.
26. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Rall TW, Nies AS, et al. Goodman and Gilman's the pharmacological basis of therapeutics. New York: Pergamon Press, 1990:383.
27. Waalinder J, Feighner JP. Novel selective serotonin reuptake inhibitors, part I. J Clin Psychiatry 1992; 53:107–12.
28. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa: a multicenter, placebo-controlled, double-blind trial. Arch Gen Psychiatry 1992; 49: 139–47.
29. Markovitz PF, Calabrese JR, Schulz SC, et al. Fluoxetine in the treatment of borderline and schizotypal personality disorders. Am J Psychiatry 1991; 148:1064–7.
30. Jenike MA, Buttolph L, Baer L, et al. Open trial of fluoxetine in obsessive-compulsive disorder. Am J Psychiatry 1989; 146:909–11.
31. McCoombs JS, Nichol MB, Stimmel GL. The cost of antidepressant drug failure: a study of antidepressant use patterns in a Medicaid population. J Clin Psychiatry 1990; 51(suppl 6):60–71.
32. Stokes PE. Fluoxetine: a five-year review. Clin Ther 1993; 15: 216–43.
33. Dilsaver SC, Greden JF, Snider RM. Antidepressant withdrawal syndromes: phenomenology and pathophysiology. Int Clin Psychopharmacol 1987; 2:1–19.
34. Dilsaver SC, Greden JF. Antidepressant withdrawal phenomena. Biol Psychiatry 1984; 19:237–56.
35. Bialos D, Giller E, Jatlow P, et al. Recurrence of depression after discontinuation of long term amitriptyline treatment. Am J Psychiatry 1982; 139:325–9.
36. Choice of an antidepressant. Med Lett Drugs Ther 1993; 35: 25–6.
37. Montgomery SA. Clinical studies of fluoxetine in depression. Int Clin Psychopharmacol 1989; 4(suppl 1):112–9.
38. Doogan DP, Caillard V. Sertraline in the prevention of depression. Br J Psychiatry 1992; 160:217–22.
39. Cole JO. New directions in antidepressant therapy: a review of sertraline, a unique serotonin reuptake inhibitor. J Clin Psychiatry 1992; 53:333–40.
40. Grahame-Smith DG. Serotonin function in affective disorders. Acta Psychiatr Scand 1989; 80(suppl 350):7–12.
41. Gjerris A, Sorensen AS, Rafaelsen OJ. 5-HT and 5-HIAA in cerebrospinal fluid in depression. J Affect Disord 1987; 12:13–22.
42. van Praag HM. Affective disorders and aggression disorders: evidence for a common biological mechanism. Suicide Life Threat Behav 1986; 16:103–32.
43. Asberg M, Bertilsson L, Martensson B. CSF monoamine metabolites in melancholia. Acta Psychiatr Scand 1984; 69:201–19.
44. Sarrias MJ, Artigas F, Martinez E. Decreased plasma serotonin in melancholic patients: a study with clomipramine. Biol Psychiatry 1987; 22:1429–38.
45. Rogeness GA, Mitchell EL, Custer GJ. Comparison of whole blood serotonin and platelet MAO in children with schizophrenia and major depressive disorder. Biol Psychiatry 1985; 20:270–5.
46. Richelson E. Antidepressants and brain neurochemistry. Mayo Clin Proc 1990; 65:1227–36.
47. Langer SZ, Galzin AM. Studies on the serotonin transporter in platelets. Experientia 1988; 44:127–30.
48. Slotkin TA, Whitmore WL, Barnes GA. Reduced inhibitory effect of imipramine on radiolabeled serotonin uptake into platelets in geriatric depression. Biol Psychiatry 1989; 25:687–91.
49. Lemberger L, Bergstrom RF, Wolen RL, et al. Fluoxetine: clinical pharmacology and physiologic disposition. J Clin Psychiatry 1985; 46(3 Pt 2):14–9.
50. Wright CE, Sasher-Sisson TA, Steenwyk RC, et al. A pharmacokinetic evaluation of the combined administration of triazolam and fluoxetine. Pharmacotherapy 1992; 12:103–6.
51. Heym J, Koe BK. Pharmacology of sertraline: a review. J Clin Psychiatry 1988; 49(suppl):40–5.
52. Richelson E. Synaptic pharmacology of antidepressants: an update. McLean Hosp J 1988; 13:67–88.
53. DeVane CL. Pharmacokinetics of the selective serotonin reuptake inhibitors. J Clin Psychiatry 1992; 53(suppl 2):13–20.
54. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991; 148:705–13.
55. Boyer WF, Feighner JP. An overview of paroxetine. J Clin Psychiatry 1992; 53(suppl 2):3–6.
56. Physicians' desk reference. Montvale, NJ: Medical Economics Press, Inc, 1993.
57. Psychopharmacologic drugs. In: Drug evaluations subscription. Chicago: American Medical Association, 1992.
58. Kreider MS, Bushnell WD, Wheadon DE. A double-blind, randomized study to provide safety information on switching fluoxetine treated patients to paroxetine without an intervening washout period [poster]. Presented at the 31st annual meeting of the American College of Neuropsychopharmacology, Puerto Rico, November 1992.
59. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990; 147:207–10.
60. Beasley CM, Dornseif BE, Bosomworth JC. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991; 303:685–92.
61. US Food and Drug Administration. Antidepressant update. Rockville, Md: US Department of Health and Human Services, 1991. DHHS publication No. 5:64–91.
62. Tulloch IF, Johnson AM. The pharmacologic profile of paroxetine, a new selective serotonin reuptake inhibitor. J Clin Psychiatry 1992; 53(suppl 2):7–12.
63. Dunbar GC, Cohn JB, Fabre LF. A comparison of paroxetine, imipramine and placebo in depressed outpatients. Br J Psychiatry 1991; 159:394–8.
64. De Wilde J, Spiers R, Mertens C, et al. A double blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand 1993; 87:141–5.
65. Sheehan D. The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacol Bull 1992; 28: 139–43.
66. Peselow ED. The short and long-term efficacy of paroxetine HCl: B. Data from a double-blind crossover study and from a year-long term trial vs imipramine and placebo. Psychopharmacol Bull 1989; 25:272–6.
67. Byrne MM. Meta-analysis of early phase II studies with paroxetine in hospitalized depressed patients. Acta Psychiatr Scand 1989; 80(suppl):138–9.
68. Kuhs H, Rudolf GAE. Cardiovascular effects of paroxetine in depressed outpatients. Biol Psychiatry 1991; 29(suppl):256–7.
69. Boyer WF, Blumhardt CL. The safety profile of paroxetine. J Clin Psychiatry 1992; 53(suppl 2):61–6.
70. Thomas DR, Nelson DR, Johnson AM. Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxy-tryptamine uptake inhibitor. Psychopharmacol 1987; 93:193–200.
71. Dunner DL, Dunbar GC. Optimal regimen for paroxetine. J Clin Psychiatry 1992; 53(suppl 2):21–6.
72. DeChant KL, Clissold SP. Paroxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 1991; 41:225–53.
73. Doogan DP, Caillard V. Sertraline: a new antidepressant. J Clin Psychiatry 1988; 49(suppl):46–51.
74. Fabre LF. A double-blind, multicenter study comparing the safety and efficacy of sertraline with placebo in major depression [poster]. Presented at the 5th World Congress of Biological Psychiatry, Florence, Italy, 1991.
75. Reimherr FW, Chouinard G, Cohn CK, et al. Antidepressant efficacy of sertraline: a double-blind, placebo and amitriptyline

controlled multicenter comparison study in outpatients with major depression. J Clin Psychiatry 1990; 51(suppl B):18–27.
76. Cohn CK, Shrivastava R, Mendels J, et al. Double blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. J Clin Psychiatry 1990; 51(suppl B):28–33.
77. Hindmarch I, Bhatti JZ. Psychopharmacological effects of sertraline in normal, healthy volunteers. Eur J Clin Pharmacol 1988; 35:221–3.
78. Fisch C, Knoebel S. The effects of sertraline on the electrocardiogram in non-elderly and elderly patients with major depression [poster]. Presented at the 5th World Congress of Biological Psychiatry, Florence, Italy, 1991.
79. Sommi RW, Crismon ML, Bowden CL. Fluoxetine: a serotonin-specific, second-generation antidepressant. Pharmacotherapy 1987; 7:1–15.
80. Aranow RB, Hudson JL, Pope HG. Elevated antidepressant plasma levels after addition of fluoxetine. Am J Psychiatry 1989; 146:911–3.
81. Preskorn SH, Alderman J, Chung M, et al. Desipramine levels after sertraline or fluoxetine [abstract]. Abstract presented at the annual meeting of the American Psychiatric Association, Washington, DC, 1992.
82. Goff DC, Midha KK, Brotman AW, et al. Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. Am J Psychiatry 1991; 148:790–2.
83. Pearson HJ. Interaction of fluoxetine with carbamazepine. J Clin Psychiatry 1990; 51:126–8.
84. Grimsley SR, Jann WM, Carter JG, et al. Increased carbamazepine plasma concentrations after fluoxetine coadministration. Clin Pharmacol Ther 1991; 50:10–5.
85. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid. J Clin Psychopharmacol 1991; 11: 389–94.
86. Reimheer FW, Wood DR, Byerley B, et al. Characteristics of responders to fluoxetine. Psychopharmacol Bull 1984; 20:70–2.
87. Beasley CM Jr, Sayler ME, Cunningham GE, et al. Fluoxetine in tricyclic refractory major depressive disorder. J Affect Disorder 1990; 20:193–200.
88. Lader M. Fluoxetine efficacy vs comparative drugs: an overview. Br J Psychiatry 1988; 153(suppl 3):51–8.
89. Montgomery SA, Dufour H, Brion S. The prophylactic efficacy of fluoxetine in unipolar depression. Br J Psychiatry 1988; 153(suppl 3):69–76.
90. Schatzberg AF, Cole JO. Manual of clinical psychopharmacology. Washington, DC: American Psychiatric Press, Inc, 1991.
91. Montgomery SA. The efficacy of fluoxetine as an antidepressant in the short and long term. Int Clin Psychopharmacol 1989; 4(suppl 1):113–9.
92. Wernicke JF. The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985; 46:59–67.
93. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. J Clin Psychiatry 1991; 52:491–3.
94. Fava M, Rosenbaum JF, Cohen L, et al. High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. J Affect Disord 1992; 25:229–34.
95. Beasley CM Jr, Bosomworth JC, Wernicke JP. Relationships among dose, response, adverse events and plasma concentration in the treatment of depression. Psychopharmacol Bull 1990; 26:18–24.
96. Stoll AL, Pope HG, McElroy SL. High dose fluoxetine: safety and efficacy in 27 cases. J Clin Psychopharmacol 1991; 11: 225–6.
97. Schweizer E, Rickels K, Amsterdam JD, et al. What constitutes an adequate antidepressant trial for fluoxetine? J Clin Psychiatry 1990; 51:8–11.
98. Cain JW. Poor response to fluoxetine: underlying depression, sertonergic overstimulation, or a "therapeutic window." J Clin Psychiatry 1992; 53:272–7.
99. Fluoxetine with benzodiazepines and other sedatives. Biol Ther Psychiatry Newsletter 1993;16:11–2.
100. Lasher TA, Fleishaker JC, Steenwyk RC, et al. Pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. Psychopharmacol (Berlin) 1991;104 :323–7.
101. Devarajan S. Interaction of fluoxetine and chloral hydrate. Can J Psychiatry 1992;37:590–1.
102. Greenblatt DJ, Preskorn SH, Cotreau MM, et al. Fluoxetine impairs clearance of alprazolam but not of clonazepam. Clin Pharmacol Ther 1992; 52:479–86.
103. Jensen D. Antidepressant mythology. N Z Med J 1989; 102: 288–90.
104. Keller MB, Klerman G, Lavori PW, et al. Long term outcome of episodes of major depression. JAMA 1984; 252:788–92.
105. WHO Mental Health Collaborating Centers. Consensus statement. J Affect Disord 1989; 17:197–8.