Problems With Currently Available Antidepressants

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Although options for pharmacologic treatment for depression have grown seemingly exponentially over the past several decades, the current armamentarium of antidepressants continues to have limitations of both efficacy and tolerability. The problems include an unacceptable lack of efficacy, delayed onset of therapeutic effects, an inability to predict responses to one or another agent, drug-drug interactions, and difficulty with tolerability during both acute and chronic treatment. This article reviews the problems that persist in the use of currently available antidepressant medications and presents a list of attributes that would be characteristic of the ideal antidepressant.

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Major depression is a disorder with great personal and societal costs. It is a common illness, with an estimated lifetime prevalence of 10% to 25% for women and 5% to 12% for men.[1–3] Up to 50% of patients who experience one episode of depression will go on to have a second, and the risk increases with each subsequent episode.[4] The Global Burden of Disease Study, a collaborative effort between the Harvard School of Public Health and the World Health Organization, recently reported that major depression will be the leading cause of morbidity in developing countries in the next century.[5] The first effective pharmacologic treatments for depression, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs), revolutionized the treatment of patients who have this disorder. The availability of many new agents over the last decade or so promised a new era in treatment; however, our current armamentarium continues to have limitations of both efficacy and tolerability. Efficacy rates have not improved; most studies of antidepressant efficacy of available agents reveal a common pattern of remission in approximately 30% of patients, partial response in 40%, and no improvement whatsoever in 30%.

In this report, the currently available pharmacologic treatments for depression are reviewed with a focus on the major problems associated with their use. These problems include an unacceptable lack of efficacy, delay of onset of therapeutic effect, inability to predict response to one or another agent, drug-drug interactions, and difficulty with tolerability during both acute and chronic treatment. These issues are framed first in a general way, followed by a discussion of each of the major antidepressant classes. Requirements for effective agents in special populations such as the medically ill are also addressed. Finally, a "wish list" of what would constitute an ideal antidepressant is presented.

LIMITATIONS IN EFFICACY

As noted above, efficacy is one area in which all currently available antidepressants are less than ideal. Clinical studies required for approval of novel antidepressants are randomized, placebo controlled, and double blind and often include comparison of the new agent with an already approved and available antidepressant.[6] Such studies designed for submission to the U.S. Food and Drug Administration (FDA) customarily define treatment response as a 50% reduction in a baseline depression severity score on a standardized dimensional instrument of depression symptom severity such as the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS).[7] Placebo response is often quite high in such trials, and efficacious medications typically exhibit response rates only 25% to 30% higher than those for placebo.[8] The placebo response rate has received, not surprisingly, considerable attention. It is becoming increasingly clear that participation in a clinical trial with its multiple evaluations from physicians, research nurses, and research assistants at regular intervals is, in and of itself, therapeutic. This treatment situation differs from the time-limited visits of depressed patients to physicians in typical clinical practice.

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Response to medication, though, does not necessarily equate to remission, and a patient who is initially severely ill with depression symptoms may exhibit a marked reduction on a standardized dimensional rating scale yet experience significant residual symptomatology.[9] The limitation in efficacy remains a therapeutic barrier that must be addressed. Because efficacy among currently available antidepressants is similar across classes of agents, other factors typically guide choice of medication, including safety, convenience, medical comorbidity, pharmacokinetic profile, drug-drug interactions, and sometimes subtype of depression. More recent studies have examined response in other areas beyond traditionally measured symptoms. New clinical rating scales have been developed to try to measure improvement in other areas of functioning such as social adjustment.[10]

PROBLEMS WITH DRUG-DRUG INTERACTIONS

Drug-drug interactions are of considerable importance in the choice of antidepressant medication because many patients with depression have comorbid medical and psychiatric illnesses, which require medication in addition to the antidepressant. Bingefors and colleagues[11] studied the concurrent use of psychotropic and nonpsychotropic medications in adult patients in a database in the United Kingdom both before and after initiation of antidepressant medication. The mean number of prescriptions for nonpsychotropic medications in patients in the year after initiation of antidepressant therapy was 8.9. This finding underscores both the extensive medical comorbidity in these patients and the importance of potential medication interactions.

Drugs may interact with each other pharmacodynamically and/or pharmacokinetically. Pharmacodynamic interactions occur at the cellular and intracellular level when medications have similar or opposing mechanisms of action.[12] An important example of this is the interaction that occurs when an MAOI and a selective serotonin reuptake inhibitor (SSRI) are coadministered. Both medications increase serotonin (5-HT) concentrations at the synapse, and when they are used in combination, the serotonin syndrome may result.[13] This syndrome is characterized by tachycardia, hyperactivity, hypertension, gastrointestinal distress, tremulousness, hyperthermia, sweating, mental status changes, myoclonus, and, in its most serious form, cardiovascular collapse.[14] This syndrome is a dramatic example of a pharmacodynamic interaction. Less severe pharmacodynamic interactions can also occur, resulting in worsened side effects when an antidepressant is used with another medication with a similar side effect profile. For example, the combination of a TCA and another medication with anticholinergic properties can cause an increase in anticholinergic side effects such as confusion, dry mouth, and constipation.[15]

Pharmacokinetic interactions occur when one medication affects the absorption, distribution, metabolism, or excretion of another drug.[12] Most psychotropic medications, antidepressants included, are metabolized via the hepatic cytochrome P450 isoenzyme system. Emerging literature on the enzymes of this system has yielded information of clinical importance in the prescription of medications, including antidepressants. Several of these hepatic enzymes exhibit genetic polymorphism, i.e., differences between individuals in the presence and quantity of certain isoenzymes.[16] For example, a subset of the population (5%–7% of white individuals) are deficient in the cytochrome P450 2D6 (CYP2D6) enzyme subtype and subsequently are limited in their ability to metabolize certain drugs through this system.[17] Thus, they may develop very high serum medication levels at low doses of medication metabolized through this pathway.

Of particular importance is the realization that certain medications inhibit one or more hepatic isoenzymes. Administration of these drugs can inhibit metabolism of other drugs that are substrates for these enzymes. Specific examples of this phenomenon are discussed below. As more is understood about this enzyme system, its genetic polymorphism, and the in vivo implications of drug metabolism, clinicians may have better guidelines about choice of medications in particular clinical circumstances.[16] Despite concerns that antidepressants that inhibit one or another cytochrome P450 isoenzyme would result in large numbers of severe and perhaps even lethal drug-drug interactions,[18] data supporting such a poor outcome have not been realized.

REVIEW OF CURRENTLY AVAILABLE ANTIDEPRESSANTS

Tricyclic Antidepressants

The TCAs were serendipitously discovered during the search for new and safer antipsychotic agents. The first among these was imipramine, which was noted to have antidepressant effects in schizophrenic patients.[19] The efficacy of these antidepressants has been proven in multiple, adequately controlled studies, and even to the present time imipramine and related TCAs have remained the "gold standard" for antidepressant efficacy. The rate of response (50% or greater decrease in depression severity) to TCAs is typically 60% to 70%, whereas that for a true remission (i.e., no residual symptomatology) is approximately 40%.[13]

The TCAs have a high affinity for many central nervous system (CNS) receptors, including muscarinic, cholinergic, histaminergic, α-adrenergic, and dopaminergic receptors, as well as for the 5-HT and norepinephrine (NE) transporters. The drugs within this class vary somewhat in their affinities for different receptors, but their clinical effects and side effect profiles are more similar than differ-

ent.[15] The antidepressant effect of the TCAs is attributed to their inhibition of NE and 5-HT transporters; their effects on other receptors are thought to be responsible for their multitude of side effects.[20]

Anticholinergic side effects are the most common side effects experienced by patients treated with TCAs. These include dry mouth, urinary retention, constipation, tachycardia, and blurred vision.[15] Aggravation of narrow-angle glaucoma in susceptible patients may also occur. CNS anticholinergic effects can result in cognitive dysfunction and delirium. Sedation and weight gain are common and are thought to be secondary to the antihistaminic effects of the TCAs.[13,19,21,22] The anticholinergic effects alone render these medications relatively contraindicated in certain comorbid medical illnesses, including glaucoma, prostatic hypertrophy, coronary artery disease, and dementia.

The cardiovascular effects of the TCAs account for the most potentially dangerous side effects of this class of drugs. The TCAs are known to have quinidine-like effects on the heart and can cause cardiac conduction delays, particularly first-degree atrioventricular and bundle branch block.[23] The mechanisms for this are not well understood, but are likely due to a sodium channel blockade.[23] The therapeutic index for these medications is low; therefore, some patients may develop toxicity at therapeutic doses and blood levels.[19] Because of this phenomenon and the potential cardiotoxicity of the TCAs, the risk of toxicity from intentional and unintentional overdose cannot be overemphasized. TCAs remain the number one class of prescription medication most responsible for death by poisoning in the United States.[19] A study in South Australia by Battersby and colleagues[24] examined deaths by antidepressant overdose from 1986 to 1990. In their sample of 71 deaths (65 suicides), amitriptyline, doxepin, and dothiepin were the 3 most frequently lethal antidepressants. Remarkably, 43% of this sample had a history of previous suicide attempts. This study underscores the ongoing risk in prescribing such potentially toxic medications to depressed patients who are already at high risk for suicide. In the United States, the pressures of managed care have resulted in markedly shortened inpatient lengths of stay and, correspondingly, a greater risk for suicidality among outpatients.

Toxicity may also occur because of pharmacodynamic and pharmacokinetic drug-drug interactions. Metabolism of TCAs occurs primarily but not exclusively by the CYP2D6 isoenzyme. When TCAs are coadministered with inhibitors of this enzyme (such as the SSRIs fluoxetine, sertraline, or paroxetine), serum levels of the TCA can increase markedly,[16] sometimes as much as 4-fold.[18]

Orthostatic hypotension attributed to blockade of α-adrenergic receptors is a common and potentially severe side effect of the TCAs. An orthostatic fall in systolic blood pressure of 26 mm Hg on average, independent of age or heart disease, has been reported in patients treated with imipramine.[25] In 20% of patients in this study, this side effect "significantly affected therapy," and a retrospective analysis indicated the rate of injury from falls to be 4%. The use of these medications in the elderly has been associated with increased risk of hip fracture, most likely secondary to orthostatic hypotension.[26] Some investigators have suggested that orthostatic hypotension may be a more prominent problem with TCAs than conduction problems in patients with preexisting cardiac disease.[23]

Less common side effects of the TCAs include extrapyramidal symptoms,[27] hyperprolactinemia, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[28] Sexual dysfunction is not uncommon with these medications, although it does not appear to be as frequent as with some of the newer antidepressants.[29,30] The aforementioned less-than-optimal side effect profile of the TCAs is associated with both unacceptable noncompliance rates and a dropout rate as high as 20%.[31] It is likely that these medications are often underdosed because of side effects and concerns about toxicity, particularly in primary care settings.[32]

Monoamine Oxidase Inhibitors

The antidepressant properties of the MAOIs were first discovered during trials of an antituberculosis medication, isoniazid, which was later discovered to inhibit monoamine oxidase (MAO).[14] The MAOIs currently available in the United States, phenelzine, isocarboxazid, and tranylcypromine, are nonselective and irreversible. They block both the A and B forms of the MAO enzyme and permanently inactivate it. The antidepressant action of the MAOIs is thought to be due to their potentiation of monoaminergic neurotransmission. Their efficacy has been well established, and evidence suggests that they show a distinct advantage in treatment of one specific subtype of depression,[33] so-called "atypical depression," characterized by increased appetite, reverse diurnal mood variation, and hypersomnia.[15]

Despite the efficacy of the MAOIs, their clinical use is limited largely because a hypertensive crisis can occur when certain medications or foods are ingested while a patient is being treated with these agents. Because of the inhibition of the MAO enzyme by the MAOIs, when pressor amines such as tyramine or sympathomimetics (e.g., pseudoephedrine) are ingested, a dangerous rise in blood pressure can occur.[19] Moreover, patients receiving MAOIs must adhere to strict dietary restrictions to limit ingestion of tyramine-containing foods such as aged meats and cheeses.

Another untoward drug-drug interaction, the so-called serotonin syndrome, can occur if an MAOI is coadministered with another medication that increases 5-HT concentrations in the synapse.[13] Most antidepressants, including TCAs, SSRIs, and some of the newer antidepressants, increase 5-HT availability by one or another mechanism,

and thus use of such agents in combination with MAOIs is contraindicated.[15] It is important to note that MAOIs ingested in overdose may also cause this syndrome.

Other side effects of MAOIs include dizziness, orthostatic hypotension (or lowering of both supine and standing blood pressure, which can mask orthostatic hypotension; see Halper and Mann[23]), suppression of rapid eye movement sleep, weight gain, and sexual dysfunction.[15] Another limitation of MAOIs is the requirement for multiple daily doses.

Moclobemide is a reversible, selective MAO type A inhibitor, which is available outside the United States. Its efficacy over placebo has been shown to be statistically significant,[34] although evidence for equal efficacy when compared with irreversible MAOIs in treating atypical or treatment-refractory depression is lacking. Some evidence is accumulating that it is effective in the treatment of dysthymia[35]: one double-blind study compared placebo, moclobemide, and imipramine in outpatients with dysthymia and major depression (so-called "double depression") or dysthymia alone. Moclobemide was superior to placebo and equally efficacious to imipramine in dysthymia; it was superior to both placebo and imipramine in double depression. Moclobemide carries a lower risk of tyramine toxicity[34] than the nonselective, irreversible MAOIs, but its use at higher doses may still require some dietary restrictions. The most common side effects of moclobemide are appetite loss, insomnia, and nausea.[19]

Selective Serotonin Reuptake Inhibitors

The SSRIs were introduced for use in the United States between 1988 and 1998 and are potent and relatively selective inhibitors of 5-HT reuptake at presynaptic terminals.[36] Five SSRIs are currently marketed in the United States (in order of release): fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. There is little doubt that the SSRIs represent an improvement in antidepressant treatment, particularly in terms of safety and tolerability. However, they are not without their limitations.

Efficacy of the SSRIs relative to older antidepressants, particularly TCAs, has been the topic of considerable study and debate. Although some studies have shown differences in efficacy for one drug compared with another, all antidepressants are generally thought to possess similar efficacy for patients with major depression.[19,36–38] However, a few well-controlled studies conducted by the Danish University Antidepressant Group (DUAG) have suggested that although response rates are similar between SSRIs and TCAs in patients with major depression, remission rates are lower with SSRIs.[39,40] This purported advantage of TCAs over SSRIs may be due to the advantages of the former agents in severe or refractory depression.

The documented efficacy of the SSRIs taken together with their more tolerable side effect profile when compared with the older medications and their great margin of safety render them first-line agents.[13,41] Although the SSRIs share a similar side effect and pharmacodynamic profile, marked differences in their pharmacokinetic profiles and their action at nonserotonin CNS sites are of potential clinical significance.[13,36] The most common side effects of the SSRIs are attributable to increased 5-HT synaptic activity: nausea, headache, insomnia, nervousness/agitation, and sexual dysfunction. In clinical practice, patients may experience different side effects with different SSRIs.[19,36] Rare side effects include extrapyramidal symptoms such as akathisia,[27] nonpuerperal lactation,[42] and lowering of seizure threshold.[15]

The most potentially dangerous problem in use of the SSRIs is the previously described serotonin syndrome, which can occur when these agents are combined with other serotonin-potentiating agents, including MAOIs.[14,43] The combination of SSRIs and MAOIs is absolutely contraindicated. A 2-week (and up to 6-week for fluoxetine) washout period should be initiated after discontinuation of an SSRI before MAOI therapy is prescribed.[36]

SSRIs differ in their pharmacokinetic profiles in (1) half-life, (2) presence or absence of metabolites, (3) capacity to inhibit one or another of the cytochrome P450 isoenzymes, and (4) protein binding. Fluoxetine has the longest half-life at 2 to 3 days for the parent compound and 7 to 9 days for its active metabolite, norfluoxetine.[36] The half-lives of the other compounds in this class range from 12 to 30 hours.[36] Protein binding varies among these compounds from approximately 80% for fluvoxamine and citalopram to 95% or greater for fluoxetine, sertraline, and paroxetine.[15]

Drug-drug interactions may occur with one or another of these medications because of their inhibition of one or more cytochrome P450 isoenzymes. The CYP1A2 isoenzyme metabolizes theophylline, clozapine, and caffeine; its inhibition by fluvoxamine increases concentrations of these drugs, with resultant potential toxicity.[12] Fluoxetine (and its metabolite, norfluoxetine), sertraline, and paroxetine are all inhibitors of the CYP2D6 isoenzyme and therefore may cause elevations in plasma concentrations of nortriptyline, desipramine, and other TCAs.[18] The CYP2C6 isoenzyme metabolizes phenytoin and diazepam, among other medications, and fluoxetine, sertraline, and fluvoxamine all inhibit this enzyme.[16] Fluvoxamine, fluoxetine, and sertraline can theoretically inhibit the CYP3A4 isoenzyme, which could result in untoward interactions with terfenadine, astemizole, carbamazepine, and several benzodiazepines, although there is little evidence that the latter 2 SSRIs do so in vivo.[16]

Sexual side effects are arguably the most significant problem associated with the long-term use of SSRIs.[44] Estimates of frequency of sexual side effects with SSRIs vary widely, and the package insert data grossly underestimate the prevalence of sexual side effects because they are based on spontaneous reports.[30,44] A confounding factor is that

sexual dysfunction is common in depressive illness.[45,46] In fact, the DSM-IV criteria for major depression include decreased desire or interest in sexual behavior as a feature of depression.[47] Clinical experience and systematically conducted research since the SSRIs became widely used have brought to light the significant side effect burden of sexual dysfunction. Montejo-González and colleagues[30] studied 344 outpatients treated with fluoxetine, paroxetine, sertraline, and fluvoxamine, primarily for mood disorders. Only patients with no previous history of sexual dysfunction were included. A much higher rate of sexual dysfunction was found by using a questionnaire when compared with spontaneous patient reports. In general, high rates of sexual dysfunction were reported for all of the SSRIs studied. Remarkably, 81.4% of patients experienced no improvement in sexual dysfunction over the 6-month period of treatment. Other smaller studies have identified delay in orgasm or ejaculation after SSRI treatment, although some patients in each study reported increased libido.[44,46] One recent study of fluvoxamine in healthy volunteers showed a variety of sexual side effects after 2 to 4 weeks of therapy, consistent with effects found with other SSRIs[48]; in contrast, Nemeroff and colleagues[49] reported a lower frequency of sexual dysfunction with fluvoxamine compared with sertraline. Overall, sexual side effects from SSRIs are a problem that patients generally underreport. These effects may well affect compliance and surely have a negative impact on patients' overall quality of life.

Dual Reuptake Inhibitors: Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine is the first representative of a new class of antidepressants, the serotonin-norepinephrine reuptake inhibitors (SNRIs). It is an inhibitor of reuptake of 5-HT and NE, and a weak reuptake inhibitor of dopamine. Interestingly, there is considerable evidence that paroxetine is a more potent SNRI than venlafaxine in vitro[50] and, moreover, that nefazodone is an SNRI as well, although the latter drug's primary action appears to be its blockade of the 5-HT_2 receptor.[50] The considerably lower protein binding of venlafaxine (27%) and its major metabolite (30%) and its higher dose range (75–375 mg/day) compared with paroxetine (95% and 20–50 mg, respectively) may render it a more effective NE reuptake inhibitor in vivo. Clearly comparative data in preclinical and clinical studies are needed. Venlafaxine has no appreciable affinity for muscarinic, cholinergic, histaminic, or α-adrenergic receptors.[15,51] It is at least as efficacious as TCAs and SSRIs in the treatment of depression. Some data suggest that venlafaxine may be more effective than SSRIs in severe depression and treatment-resistant depression.[36,41,52] It has also been suggested to have a more rapid onset of therapeutic effect than other antidepressants.[34]

The half-life of venlafaxine is 5 hours; it has one active metabolite, *O*-desmethylvenlafaxine, which has a half-life of 11 hours. Venlafaxine is available in an extended-release form, which allows once-a-day dosing. It is metabolized by the CYP2D6 and CYP3A3/4 isoenzymes and thus may exhibit interactions with other medications also metabolized by these enzymes.[16] Not surprisingly, therefore, venlafaxine increases plasma haloperidol concentrations. The most commonly reported side effects include nausea, anorexia, insomnia, nervousness, asthenia, sweating, constipation, dry mouth, dizziness, tremor, and blurred vision. Side effects that seem to be dose-related and apparently related to both venlafaxine's serotonergic and noradrenergic effects include nausea, diastolic hypertension, sexual dysfunction, somnolence, and sweating.[15]

An important and relatively unique side effect of venlafaxine is a dose-dependent increase in blood pressure.[34] Therefore, blood pressure monitoring is appropriate during treatment with venlafaxine, especially at higher doses when the risk is higher. Increases in heart rate and plasma cholesterol concentrations have also been observed with venlafaxine treatment. The clinical significance of the latter side effects remains obscure.

Other Antidepressants

Nefazodone and trazodone. Trazodone was the first of a class of antidepressants that blocked the neuronal reuptake of 5-HT and NE, albeit weakly, but it is a potent 5-HT_2 receptor antagonist. Premarketing clinical trials demonstrated equivalent efficacy to TCAs in mild-to-moderate depression,[53] but in practice it may cause excess sedation at therapeutic doses, limiting its use as a first-line agent.[19] It is more often used in low doses with SSRIs as a sedative/hypnotic agent. Significant side effects of trazodone include orthostatic hypotension and priapism, the former a common side effect, the latter rare but occasionally requiring surgical intervention.

Nefazodone is structurally similar to trazodone and is also a 5-HT and NE reuptake inhibitor, as well as a 5-HT_2 receptor antagonist.[31,34,50] Nefazodone has been reported to be superior to placebo and is as effective as imipramine and fluoxetine in double-blind, controlled trials.[19] Some studies indicate a superior response to SSRIs at higher doses of nefazodone, e.g., > 500 mg/day.[19] A recent landmark study of patients with chronic depression compared monotherapy with nefazodone or cognitive-behavioral therapy (CBT) with the combination.[54] The monotherapies, nefazodone and CBT, were equally effective in regard to response and remission rates; the combination treatment was superior to either monotherapy. Common side effects of nefazodone include nausea, somnolence, dry mouth, dizziness, asthenia, and constipation.

Nefazodone produces at least 3 metabolites of varying activity; each of these, like the parent compound, has a short half-life.[36] Because of this short half-life, nefazodone requires twice-a-day dosing. Drug-drug interactions

are of potential significance in the use of nefazodone because it is an inhibitor of the CYP3A4 isoenzyme.[31] This enzyme is important in the metabolism of alprazolam, triazolam, haloperidol, several antihypertensive medications, antivirals for human immunodeficiency virus (HIV) infection, and MAOIs.[55] Thus, when nefazodone is coadministered with a benzodiazepine such as alprazolam or triazolam, the plasma concentration of the benzodiazepine is increased.[31]

Bupropion. Bupropion is the only representative of a unique class of antidepressants. It is a relatively weak inhibitor of dopamine, NE, and 5-HT reuptake. Whether these effects are responsible for the antidepressant action of bupropion remains unknown. Its efficacy is comparable to that of TCAs in depressed inpatients and outpatients.[56] Bupropion is also unique because it is effective in smoking cessation and is FDA-approved for this indication.[57] The most dangerous side effect of bupropion is its increase in seizure risk, which was initially identified in nondepressed, bulimic patients.[19] This risk seems highest in patients with a history of seizure or head trauma or in patients taking other medications that lower seizure threshold.[15] The sustained-release form of bupropion has markedly reduced the risk of seizure to that of other antidepressants. High dose or high plasma level of the drug increases the risk of seizure. The most common side effects of bupropion are anxiety, agitation, and insomnia, although appetite suppression may also occur. Development of mania and psychotic symptoms in susceptible patients has been suggested to be more frequent with bupropion than with other antidepressants, possibly because of its dopamine reuptake inhibition,[51] although bupropion has also been suggested to be the drug of choice for bipolar depression.[58] The entire clinical database on the use of bupropion in bipolar depression is quite small.

The half-life of bupropion is 14 hours, and its 2 principal active metabolites have half-lives of approximately 24 hours.[36] Despite these long half-lives and the availability of the sustained-release form, total daily bupropion dose should be divided to minimize the seizure risk. The maximum recommended total dose is 450 mg/day.[13]

Mirtazapine, a noradrenergic and serotonergic receptor modulator. Mirtazapine is a tetracyclic antidepressant, thought to act by 2 modes of action: receptor blockade at α_2-adrenergic receptors, which results in increased NE and 5-HT release, and blockade at 5-HT_2 and 5-HT_3 receptors.[34] Its efficacy has been shown to be at least equivalent to that of amitriptyline in depressed inpatients and outpatients.[19,36] Mirtazapine has a very low affinity for dopamine and cholinergic receptors, but it does have a relatively high affinity for the histamine H_1 receptor. Antagonism at this receptor appears to mediate its most common side effects of sedation, fatigue, increased appetite, and weight gain.[36] The weight gain is generally considered the most problematic. Other, less common side effects include transient neutropenia, transient elevations in liver enzyme levels, and elevated serum cholesterol.[19] Rare severe neutropenia has been reported in patients taking mirtazapine, but a causal relationship has not been established.[15] It apparently causes no sexual dysfunction. Detailed data on drug interactions with mirtazapine are not available, but in vitro studies and clinical experience suggest that it does not inhibit any of the cytochrome P450 isoenzymes.[52]

Norepinephrine Reuptake Inhibitors

Reboxetine is a relatively new antidepressant and is the first selective non-TCA NE reuptake inhibitor (NRI).[59] Although not yet available in the United States, it is expected to be approved by the FDA in the near future. It is currently marketed in the United Kingdom and other European countries. Its efficacy has been documented in the treatment of major depression in short-term and long-term studies.[60] It appears to be at least as efficacious as TCAs and SSRIs and may, like venlafaxine, have superior efficacy in severe depression[61] and perhaps a more rapid onset of action.[60] Clinical trials with reboxetine have utilized the Social Adaptation Self-evaluation Scale (SASS), a novel tool to evaluate outcomes distinct from those traditionally measured in efficacy studies of depression.[10] It measures social functioning, relationships, and self-perception. The validity, reliability, and sensitivity of this scale have been established, and it apparently measures variables not included in the HAM-D.[62] In a double-blind, randomized, placebo-controlled study, reboxetine-treated patients exhibited greater improvement as assessed with the SASS[63] when compared with patients treated with placebo or fluoxetine at 1 month of treatment. The most common side effects of reboxetine in clinical trials are dry mouth, headache, nausea, sweating, constipation, and hypotension.[61] Reboxetine does not inhibit any of the cytochrome P450 isoenzymes thus far studied, including the 1A2, 2C9, 2D6, 2E1, or 3A4 subtypes.[64]

FUTURE NEEDS

Improved Efficacy

Although options for pharmacologic treatment for depression have grown seemingly exponentially over the past several decades with both the introduction of new agents and combination pharmacotherapy, the available treatments have significant limitations. Potential major advances include a more rapid rate of therapeutic onset, improved efficacy (particularly in treating certain depression subtypes), greater tolerability, and improved safety in special populations.

Onset of action of antidepressants has traditionally been viewed as requiring on average 4 to 6 weeks; therefore, potential FDA registration studies of clinical efficacy focus on a 6- to 8-week time scale. Earlier response, while

not uncommon in clinical trials, has typically been attributed to a placebo effect. Placebo response and true drug response are assumed to be mutually exclusive in the same patient, and early responders are usually dropped from a study.[7] This separate placebo response in part led to the addition of placebo lead-in periods prior to random assignment of patients to active treatments. The design of most standard clinical trials may limit their ability to detect a more rapid clinical response.[7] Some authors suggest that use of survival analysis, which emphasizes time to response, is a superior method of detecting early response when compared with more conventional approaches.[7,60] Stassen and colleagues[7] conducted a meta-analysis of several double-blind, placebo-controlled clinical trials (e.g., amitriptyline/oxaprotiline/placebo and imipramine/moclobemide/placebo). They focused on a survival analysis to seek differences in onset and time course of improvement for drug versus placebo. Their method showed early onset of action for all treatment modalities, including placebo. Most patients (> 75%) who improved within 4 weeks had also shown response within the first 14 days. The difference in efficacy between medication and placebo was found in the total number of patients who improved or responded; however, patterns of response did not differ. These findings contrast with the traditional view that onset of action of antidepressant medication does not occur before 4 to 6 weeks. It also refutes the notion that pattern of response can differentiate "true" response from placebo response. In this era of managed care and its associated marked reduction in inpatient hospital lengths of stay, a faster rate of response would be of great significance.

Differential Responses for Subtypes of Depression

Antidepressants are routinely approved by the FDA with the sole therapeutic indication being treatment of major depression. However, the existence of several distinct subtypes of depression and other affective disorders has enormous clinical importance in terms of treatment response. Dysthymic disorder (or dysthymia) is an illness characterized by a persistent low mood not severe enough to fulfill criteria for major depression. It is estimated that 3% to 6% of the population experiences dysthymia.[65] Several controlled studies of antidepressants have revealed their superior efficacy to placebo in the acute treatment of dysthymia.[35,65] Notably, little is known about the long-term efficacy of antidepressants in this disorder. Because of the chronic nature of dysthymia, long-term safety and tolerability of antidepressants are especially important issues in patients with this illness.

The data on treatment of severe depression, or the melancholic subtype, are difficult to assess because clinical trials of major depression vary widely in their inclusion of patients with severe depression and in the minimal severity criteria for inclusion. The SNRI venlafaxine and TCAs may have some advantage over SSRIs,[9] but the data supporting this hypothesis are far from ironclad.

An estimated 15% of episodes of major depression fulfill criteria for the psychotic subtype.[66] Coryell and colleagues[67] studied patients with major depression with and without psychotic features over a 10-year period to characterize their patterns of illness and impairment. Their study population comprised 144 patients with psychotic features and 643 patients without psychotic features. Presence of psychotic features did predict higher levels of symptom severity and overall greater levels of impairment. These patients also tended to experience longer episodes with shorter interepisode intervals. Unfortunately, clinical trials scrutinizing putative new antidepressants often exclude patients with psychotic symptoms; therefore, the available efficacy data may not be generalizable to patients with psychotic depression.[8] It is well documented that patients with psychotic depression require combination antipsychotic-antidepressant treatment or electroconvulsive therapy (ECT). Reports exist, however, that fluvoxamine may be effective monotherapy for psychotic depression,[68,69] but experienced clinicians and investigators remain skeptical.

Antidepressants are frequently used in combination with mood stabilizers in the treatment of bipolar disorder. There is a risk of inducing mania in the use of any antidepressant, and there is some evidence that antidepressants may also accelerate cycling, i.e., decrease interepisode intervals, in a subset of bipolar patients.[70,71] At the current time, bupropion and SSRIs, particularly paroxetine, are considered the drugs of choice for bipolar depression, although few controlled studies have been conducted.[58]

Efficacy for Special Populations

Pregnant and lactating women. Choice of antidepressant medication during pregnancy is an important issue because women of childbearing age are at a disproportionately high risk for depression.[19,72] Up to 10% of pregnant women fulfill criteria for a mood disorder.[73] No current psychotropic medication has FDA approval for use in pregnancy,[74] and few data are available to guide the clinician in treating pregnant women. Many issues present difficulties in evaluating medications for use in pregnancy. Several large studies show rates of congenital malformation in the general population of 2% to 2.5%. It is therefore very difficult to demonstrate an association between low-frequency adverse events and use of a specific medication.[74]

Other problems include lack of control of potentially confounding variables such as age, substance abuse, and exposure to other agents. Many pregnant women are also prescribed other medications and ingest over-the-counter medications as well. The underlying CNS illness itself rather than the medication may predispose a fetus to malformations, and this is impossible to assess in postmarket-

ing drug surveillance data collection.[73] MAOIs are known animal teratogens and are thus contraindicated in pregnant women. TCAs do not seem to increase the risk of congenital malformations, but a neonatal withdrawal syndrome has been reported in the offspring of women treated with TCAs during pregnancy. Features of this syndrome are tachypnea, tachycardia, and cyanosis in the infant.[73,75] Of the newer medications, the most data are available for fluoxetine; postmarketing surveillance data suggest that no increased rate of congenital malformations is associated with fluoxetine treatment, although the registry includes only 1500 patients.[74] Long-term neurodevelopmental effects on children exposed to antidepressants in utero are lacking. Recently, Stowe and colleagues[76] have conducted the first study of placental passage of SSRIs. Although all SSRIs exhibit incomplete passage, paroxetine and sertraline showed more limited placental passage than fluoxetine.

Data have shown that virtually all psychotropic agents are excreted in breast milk and are detectable in serum of nursing infants, but the clinical significance in short-term and long-term health of these infants is unknown.[77,78] The SSRIs in order of increasing breast milk concentrations are, of those for whom such data are available, paroxetine, sertraline, and fluoxetine.

Children and adolescents. Pharmacologic treatment of childhood and adolescent depression remains controversial. Data from multiple double-blind, placebo-controlled trials have not shown efficacy of imipramine over placebo.[79] Sudden death has also been reported in children prescribed desipramine.[80] SSRIs may be more effective in the treatment of patients in this age group.[79,81] Emslie and colleagues[82] conducted the first large, multicenter, placebo-controlled trial of fluoxetine in the treatment of depression in children and adolescents. Fluoxetine was superior in efficacy to placebo. A recently completed study in depressed children and adolescents similarly demonstrated the efficacy of paroxetine and the lack of efficacy of imipramine.[83]

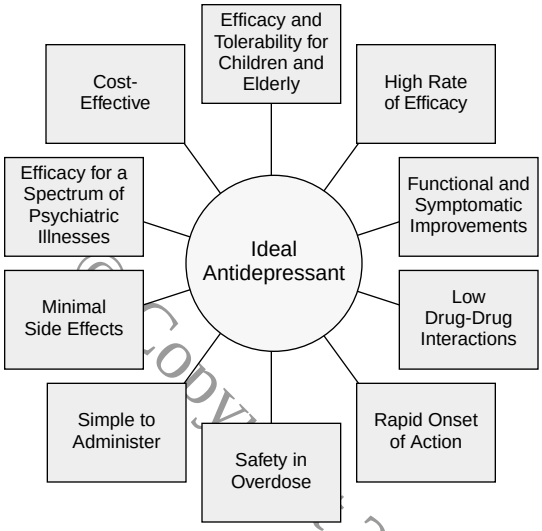
Elderly. The selection of an antidepressant for elderly patients requires special care. The elderly exhibit substantial rates of depression and inordinately high rates of suicide compared with the younger population.[84] For these reasons, and because of the now well-documented relationship between heart disease and stroke on the one hand and depression on the other, it is imperative that depression be recognized in the elderly and that safe and efficacious agents be available to treat it.[28] Rovner et al.[85] evaluated 454 consecutive patients admitted to a nursing home and followed them for 1 year. Diagnosable major depression was found in 12.6% of patients in that year and depressive symptoms, in 18.1%. The likelihood of death was 59% higher in the patients with major depression compared with those without depression. Strikingly, the majority of these patients were not treated with an antidepressant. The available data show that, in the elderly, the antidepressants thus far studied have similar efficacy in younger and older patients.[28,52]

In the elderly, safety and tolerability are of paramount importance. Adverse drug reactions account for an estimated 10% to 30% of hospitalizations of the elderly, including adverse effects and problematic drug-drug interactions.[86] Many elderly patients are prescribed multiple medications. In fact, patients 65 years and older are prescribed on average 13 medications per year.[86] Use of multiple medications markedly increases the risk of both pharmacokinetic and pharmacodynamic interactions of an untoward type.

TCAs are of special concern in the elderly for several reasons. The first is their cardiotoxicity, which is a common problem in aging patients who often have comorbid cardiac disease. The side effect profile of the TCAs renders them even less tolerable in the elderly because, as a group, the elderly are especially sensitive to both orthostatic hypotension and anticholinergic effects.[28] Moreover, the SSRIs may cause agitation, insomnia, and weight loss in the elderly.[86] In general, few data exist on the use of the newer medications in the fast-growing population of the "old-old" (patients 80 years of age and older) in the United States.

Patients with comorbid medical illness. As in the elderly, safety and tolerability of antidepressants are of paramount importance in patients with comorbid medical illness. Although the topic is too broad to address extensively here, a few relevant issues are discussed. Patients with many medical illnesses, including Parkinson's disease, HIV/acquired immunodeficiency syndrome, cancer, multiple sclerosis, diabetes, and cardiac disease, exhibit high rates of comorbidity with depression. There is accumulating evidence that depression increases morbidity and mortality in patients with coronary artery disease,[87] cancer,[88,89] and HIV.[88] Prevalence of depression in patients with Parkinson's disease may be as high as 50%,[90] and antidepressant medications are effective in this group.[91] In fact, ECT has been reported to improve both the mood and movement disorders in this population.[92] Several studies have now shown that TCAs and SSRIs have efficacy in patients with comorbid HIV infection and depression,[93–95] but dropout rates are high. Drug interactions and compliance are of considerable concern in this group of patients, who typically have complicated and burdensome medication regimens. For example, many of the protease inhibitors commonly used to treat HIV infection are metabolized by the CYP3A4 isoenzyme. For this reason, inhibitors of this enzyme such as nefazodone and fluvoxamine are contraindicated in this population. Somatic symptoms of depression in patients with cancer are often attributed to the cancer[96]; thus, depression in these patients is frequently underrecognized and undertreated. Cancer patients may also have particular difficulty taking oral medications, and the availability of non-oral agents is very limited.[97] Recognition and treatment of depression in patients with comorbid medical disorders may significantly decrease their

Figure 1. Characteristics of the Ideal Antidepressant



medical morbidity and mortality. Controlled studies in these populations are difficult, but not impossible.

SUMMARY

We have reviewed the problems that persist in the use of the currently available antidepressant medications. Great progress has surely been made in the last 30 years in the treatment of depression, but there clearly remains room for the development of new antidepressants. The ideal antidepressant (Figure 1) would have a high rate of efficacy, act quickly, and be safe, simple to administer, and without burdensome side effects. It would also be cost-effective and improve functional as well as symptomatic outcomes. Some current antidepressants have documented efficacy in other disorders, some of which are frequently comorbid with depression. TCAs have proven efficacy in the treatment of chronic pain and enuresis.[33] Several SSRIs have proven efficacy in the treatment of certain anxiety disorders, including panic disorder, social anxiety disorder, and obsessive-compulsive disorder, and have FDA indications for use in these disorders. These drugs are also likely to be effective in posttraumatic stress disorder and premenstrual dysphoric disorder. Venlafaxine is approved for the treatment of major depression and generalized anxiety disorder. Medications that have efficacy in multiple illnesses that are often comorbid (for example, depression and panic disorder, migraine and depression, or depression and chronic pain) are especially helpful in primary care settings.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), bupropion (Wellbutrin, Zyban), carbamazepine (Tegretol), citalopram (Celexa), clozapine (Clozaril and others), desipramine (Norpramin and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), isoniazid (Rifamate and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), phenytoin (Dilantin and others), reboxetine (Vestra), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), triazolam (Halcion), venlafaxine (Effexor).

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