Pharmacologic Characteristics of Ideal Antidepressants in the 21st Century

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The availability of drugs for use as antidepressants has expanded greatly in the past 2 decades. Not only has the number of drugs increased but so has the diversity in associated pharmacologic effects. Drug development for central nervous system agents is proceeding at an accelerated pace. The coming decades hold the promise for the introduction of newer antidepressants that have novel mechanisms of action, improved adverse event profiles, and expanded indications. Unfortunately, the ideal antidepressant is yet to be formulated. Pharmacologic characteristics for desirable improvements are discussed relative to the currently available drugs. *(J Clin Psychiatry 2000;61[suppl 11]:4–8)*

A little more than a decade ago, the principal drugs for treatment of depression consisted of the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs). The availability of the first selective serotonin reuptake inhibitor (SSRI) in the late 1980s ushered in an unprecedented period of new antidepressant introductions. A greater variety of antidepressants from which to choose is currently available (Table 1). The bar in drug development still needs to be set high, however, to achieve the ideal antidepressant in the 21st century. The SSRIs and newer antidepressants, such as nefazodone, mirtazapine, and venlafaxine, have been compared with the TCAs numerous times, and there is broad acceptance of the significant advantages in clinical use of these newer drugs.[1,2] This review does not provide a between- or within-class comparison of existing antidepressants but discusses some prominent pharmacologic properties that would characterize an ideal drug. To the extent that current drugs possess these properties, drug selection criteria for individual patients may be drawn from them.

AN IDEAL ANTIDEPRESSANT

Some pharmacodynamic and pharmacokinetic properties of an ideal antidepressant are listed in Table 2. This fails to be an exhaustive list. Pharmacodynamic properties are divided into efficacy characteristics and safety and tolerability characteristics. Not only must an ideal drug be effective and safe, but it should be well tolerated and contribute to a patient's sense of overall wellness. Included as ideal pharmacokinetic characteristics are the properties that would allow an antidepressant to be taken on a convenient dosing schedule and to avoid problems when taken in combination with other treatments. While currently available drugs meet some of these criteria, no single antidepressant is ideal.

Efficacy Characteristics

Cures or alleviates symptoms. No currently available drug provides a cure for depression.[3] A drug able to cure the syndrome of depression would be likely to have a very specific mechanism of action directed at altering the pathophysiology of the disorder. Presently, we have substantial accumulated evidence for the involvement of both serotonin and norepinephrine in depression. These conclusions reflect the legacy of the monoamine hypothesis of depression developed in the 1960s. Some of the most provocative recent work in this field are the studies of Delgado et al.,[4,5] in which recovered depressed patients were given a diet low in tryptophan and high in amino acids that compete with the brain uptake of tryptophan, the precursor of serotonin in the central nervous system. Depressive symptoms returned in almost 70% of the patients who had been treated with a serotonin reuptake inhibitor, whereas symptoms returned in only 20% of patients previously treated with a TCA having predominant norepinephrine reuptake inhibition, such as desipramine or nortriptyline. These results suggest that norepinephrine reuptake inhibitors are less dependent on the presence of serotonin for maintaining their antidepressant effects compared with serotonin reuptake inhibitors. However, animal data collected in the 1970s demonstrated that an intact serotonergic system was necessary in order for desipramine, the most potent of the tricyclic norepinephrine reuptake inhibitors, to cause a

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Table 1. Newer Antidepressants Currently Available or in Advanced Development

Selective serotonin reuptake inhibitors
Fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, R-fluoxetine, desmethylcitalopram
Serotonin and norepinephrine reuptake inhibitors
Venlafaxine, milnacipram
Norepinephrine reuptake inhibitors
Reboxetine
Serotonin uptake and 5-HT_2 receptor antagonists
Trazodone, nefazodone
5-HT_{1A} receptor partial agonists
Buspirone, ipsapirone, gepirone
Presynaptic dopamine receptor blockers
Amisulpride, sulpiride
Monoamine oxidase subtype selective inhibitors
Befloxatone, selegiline

Table 2. Characteristics of an Ideal Antidepressant

Efficacy characteristics
Cures or alleviates symptoms
Provides efficacy for most or all patients
Provides rapid effectiveness
Provides sustained effects with continuation/maintenance treatment
Provides consistent and predictable dose:effect relationships
Safety and tolerability characteristics
Low incidence of adverse events
Minimal overdose toxicity
Low or no impairment of cognition
Beneficial effects on wellness
Pharmacokinetic characteristics
Consistent and predictable disposition
Multiple pathways of elimination
Convenient dosing schedules
Low propensity to participate in drug-drug interactions

down-regulation in the cortex of animals.[6] Together, these results suggest that both serotonin and norepinephrine are involved in the pathophysiology of depression and the mechanisms of action of antidepressant drugs.[7]

The currently available antidepressants all either block the synaptic reuptake of serotonin, norepinephrine, or both; inhibit monoamine oxidase; or affect other presynaptic and/or postsynaptic noradrenergic receptors, serotonergic receptors, or both.[8] For the TCAs, MAOIs, and SSRIs, the net result with chronic use is an increase in serotonin neurotransmission. Future antidepressants may be developed whose pharmacology is directed at alternative neurotransmitters. For example, the involvement of γ-aminobutyric acid (GABA) in depression has been long suspected.[9] Recent evidence has been found that depressed patients demonstrated a highly significant reduction in occipital cortex GABA levels compared with healthy subjects.[10]

Another advance in the search for better treatments for depression has been the demonstration that a substance P antagonist showed antidepressant effects equivalent with paroxetine in a placebo-controlled clinical trial in mixed anxiety-depression.[11] Substance P is the most abundant neurokinin in the central nervous system and is localized in brain regions that coordinate stress responses and receive convergent monoaminergic innervation. That an antagonist of this neuropeptide's receptor should prove to be an antidepressant provides hope that future drug development will result in drugs with mechanisms of action to cure or alleviate more completely the symptoms of depression.

Provides efficacy for most or all patients. Controlled clinical trials of antidepressants demonstrate that approximately 45% to 65% of patients who are treated in a short-term outpatient trial demonstrate adequate antidepressant response.[3] A 50% decrease in the symptom rating using a 17- or 21-item Hamilton Rating Scale for Depression (HAM-D) is a commonly employed definition of response. In clinical practice, the rate of response can often be improved with the addition of behavioral interventions and longer periods of treatment. Nevertheless, many patients require treatment with a second or third antidepressant before demonstrating adequate response or remission. Some recalcitrant patients are treated with electroconvulsive therapy. Antidepressants that significantly increase the percentage of patients who demonstrate a remission of symptoms when first exposed to an antidepressant are clearly needed.

Few data indicate that prominent efficacy differences exist in the currently available antidepressants, especially in the newer drugs marketed following the availability of the TCAs.[12,13] Yet some differences have emerged in the past, and some issues are unresolved. For example, Quitkin et al.[14] demonstrated the superiority of phenelzine compared with imipramine in the treatment of atypical depression. Some clinicians suspect, primarily as a result of the Danish University Antidepressant Group studies,[15] that strongly serotonergic TCAs are more efficacious than the SSRIs for the most seriously depressed inpatients. The results of an occasional clinical trial find one antidepressant superior to another, but overall the differences appear to be modest.[16]

Provides rapid effectiveness. All currently available antidepressants demonstrate a delay in the onset of their optimal antidepressant effects. When tested against placebo in controlled clinical trials, statistically significant differences between active drug and placebo may not emerge for several weeks. Elderly patients, especially, may be slow to demonstrate a full antidepressant response. This delay in therapeutic response has been correlated previously with a slow neurochemical adaptation to monoamine reuptake inhibition in animals.[8]

Most antidepressants produce a down-regulation of β_1-adrenergic receptors using microsomal preparations from rat cerebral cortex that require chronic daily administration for a week or longer.[6] Recently, the use of pindolol in depressed patients has been promoted to decrease the time to onset of antidepressant effects by blocking presynaptic autoreceptors and thus hastening the chronic adaption to monoamine reuptake inhibition.[17] Unfortu-

nately, the overall value of this neurochemical manipulation appears equivocal as the overall degree of antidepressant efficacy has remained similar whether pindolol was used or not, although the onset of symptom relief has been improved in some patients. Nevertheless, this imaginative pharmacologic approach—using a drug that blocks presynaptic serotonin-2 ($5\text{-}HT_2$) autoreceptors to hasten chronic adaption to serotonin reuptake inhibition—offers hope that other approaches will be found to allow antidepressants to become more rapidly effective.[18]

Provides sustained effects with continuation/maintenance therapy. In relapse prevention studies in which remitted depressed patients are randomly assigned to continue active drug treatment or to receive placebo, some patients who continue to receive active drug relapse. However, the majority of patients who relapse do so in the first 6 months after randomization. Ideally, the antidepressant that results in remission of depressive symptoms would keep all patients well with continued treatment. These types of studies demonstrate the value of continuation/maintenance therapy, but they also illustrate the unfortunate reality that some remitted patients relapse despite continued treatment.[19]

Provides consistent and predictable dose:antidepressant effect relationships. The nature of highly metabolized drugs is that often a poor relationship exists between the administered dose and the resulting plasma concentration. This characteristic applies to the TCAs and most antipsychotic drugs. When TCAs were the first line of antidepressant therapy, the effective dose could range between 50 mg/day in some poor metabolizers to over 300 mg/day in the general population, despite the fact that 50 mg/day of imipramine or amitriptyline, the 2 most popular TCAs, was often defined as an adequate dose. This range of daily doses represents a 6-fold or greater variability in the dose-effect relationship. Stated as a pharmacologic characteristic, the dose-response curve of the TCAs was steep.

The newer antidepressants have a more shallow dose-response curve, i.e., the minimal dose that effectively treats 80% or more of those patients who would respond at any dose shows less variability compared with the highest dose. For example, the effective dose range of nefazodone is 300 to 600 mg/day, only a 2-fold variability.[20] A more narrow dose range, reflecting a narrow dose-effect relationship, is a desirable characteristic in order to minimize empirical dosing adjustments and to rapidly reach the effective antidepressant dose. Of course, special populations such as elderly or medically impaired patients may require drug doses outside of the usual range.[21]

Safety and Tolerability Characteristics

Low incidence of adverse events. A low incidence of adverse events and high tolerability are desirable antidepressant characteristics.[22] These properties contribute to maintaining patient compliance with the prescribed drug dosage regimen. It is doubtful that drugs completely devoid of all side effects will be developed. Even though neurochemical specificity of drugs is increasing, the widespread distribution of neuroreceptors, the primary target of antidepressants, precludes a completely region-specific pharmacologic effect. Lipid-soluble antidepressant molecules are widely distributed in tissues and may affect highly specific targets in diverse locations.

Generally, antidepressants have become more tolerable. However, patients must perceive that they are receiving a continuous benefit from taking an antidepressant to maintain compliance. This perception is especially important during the first year of treatment following remission of an episode (continuation therapy) and during maintenance therapy. Thus, as tolerability in antidepressants is improved and maintenance therapy is characterized by a low patient perception that drugs are producing pharmacologic effects, educational efforts must be preserved to maintain drug-taking behavior.

Minimal overdose toxicity. Mortality from overdose of antidepressants is of continuing concern in some countries and populations, as the sales of some highly toxic antidepressants, such as the TCAs, are high. The newer, although less affordable, antidepressants have alleviated this concern for many patients. Of increasing concern regarding safety are more subtle effects on cardiovascular health. The antidepressants that inhibit the reuptake of norepinephrine (venlafaxine, reboxetine) can increase heart rate at the upper end of their dose range. Regulatory agencies are increasingly cognizant of drug effects on heart rate, blood pressure, and cardiac conduction—reflected by increased corrected QT intervals—as part of the review of drugs in development. This is not without just concern. As the expected life span of humans increases in the 21st century, more elderly patients with cardiac and cardiovascular disease will receive treatment with the antidepressant class of drugs for mood, anxiety, and other disorders. Newer antidepressants will need to exert negligible effects on these indicators of cardiovascular health.

Low or no impairment of cognition. Currently available antidepressants exert pharmacodynamic effects on neurotransmitters that are important in memory and cognition.[18] While newer drugs have minimized the deleterious effects on cognition associated with prominent muscarinic receptor blockade, this desirable characteristic of antidepressants should become increasingly emphasized in the 21st century. The exposure of children and adolescents to antidepressants is increasing, and the avoidance of drugs that may compromise cognitive development through sedative or other effects in these special populations is necessary. The elderly are another population at risk for cognitive impairment from drugs. They often have cognitive and psychomotor performance impairments as part of their depressive symptoms. Antidepressant treatments can

correct these deficits, provided sedative and anticholinergic effects do not contribute to the preexisting condition.

Lack of discontinuation effects. Antidepressants are discontinued, sometimes abruptly, owing to medical need, inadvertent or purposeful noncompliance, or an informed decision between patient and clinician. Ideally, drugs should not cause discontinuation or withdrawal effects. This has been a clinical issue recently with the recognition that the SSRIs and other antidepressants, when abruptly stopped, can result in the precipitation of somatic and cognitive complaints best described as a discontinuation syndrome.[23] While tapering drug doses downward before stopping provides a readily effective prevention, it should be recognized that pharmacologic effects may linger, even though drug dosing is slowed or stopped. An overlooked facet of drug discontinuation is that the potential for some drugs to inhibit cytochrome P450 (CYP) enzymes and thus participate in drug-drug interactions is due to the physical presence of the drug. The longer the elimination half-life of an antidepressant, the less likely that discontinuation will result in withdrawal symptoms,[24] but the longer that enzyme inhibition occurs for those drugs that share this pharmacologic property. Fluoxetine can be expected to have an inhibitory effect on CYP2D6 for a much longer time after this drug is discontinued because of its persistence in the body from a long elimination half-life, compared with paroxetine and its more rapid elimination from the body.[25]

Beneficial effects on wellness. The efficacy of antidepressants has generally been measured as symptom relief. Quality-of-life measures, such as positive effects on productivity at work, decreased absenteeism, and improved social functioning and peer relationships, are areas that have been often overlooked. These are difficult areas of drug effects to measure, but they will become important points of differentiation in drug selection if drugs in the future are shown to preferentially affect these parameters of wellness due to specific neurochemical effects.[26] For example, the role of norepinephrine in depression is generally more associated with drive, motivation, and energy level, while the role of serotonin is more associated with impulsivity. Translating these theoretical constructs of neurochemical effects on behavior into antidepressant development is another challenge in the coming decades.

Pharmacokinetic Characteristics

Consistent and predictable disposition. Only the most salient pharmacokinetic characteristics are considered here. Properties such as linear disposition, stereochemistry, and elimination half-life have been discussed previously.[27] Ideally, drug disposition is least complicated when pharmacologically active metabolites are not produced. Metabolite concentrations in the body at sites of action are rarely similar to that of their precursors, and elimination half-lives are usually longer. This difference produces a complex and constantly changing exposure of receptors to multiple pharmacologic entities. The situation is more complex when drugs are administered as racemic mixtures of enantiomers that possess different degrees of pharmacologic activity and may be stereoselectively eliminated at different rates from the body. The likelihood that measurements of plasma drug concentration will correlate with clinical effects to provide a useful tool in dosage regimen design is increased when drugs are administered as single entities without producing active metabolites. Given the increasingly rapid rate at which new chemical entities can be screened by the pharmaceutical industry as potential antidepressants, we should see more compounds with these simplified characteristics in the future.

Multiple pathways of elimination. Most antidepressants are eliminated by being highly metabolized in the liver. This fact reflects high lipid- and low water-solubility characteristics of these agents that predict extensive tissue distribution, including in the central nervous system. Further, most antidepressants are extensively metabolized by the cytochrome P450 system of enzymes. Several enzymes show a genetic polymorphism, and individuals with null alleles have been described for CYP2D6 and CYP2C19.[28] While rare (< 1% of the population), polymorphisms of CYP3A4 have recently been described; no livers have been studied without encountering this enzyme. Thus, it would be preferable for an antidepressant that is highly metabolized by a single enzyme to be eliminated by CYP3A4 rather than CYP2D6. While metabolism by CYP3A4 is a low-affinity, high-capacity pathway, it is both inducible and inhibitable. Thus, some degree of renal clearance in an ideal antidepressant would also contribute to stability of elimination. Overall, multiple pathways of drug elimination are desirable, so that compromise in any one of these, such as hepatic disease, renal disease, or absence of metabolic ability by a specific enzyme, would have minimal impact on overall rate of elimination and avoid excessive drug accumulation.

Convenient dosing schedules. Antidepressants with elimination half-lives in the range of 15 to 30 hours are conveniently dosed on a once-daily basis. Drugs with relatively short half-lives may require multiple daily doses or formulation in sustained-release preparations. While it is doubtful that moving from a once- to twice-daily dosing schedule drastically compromises compliance, any dosing more frequent than twice daily becomes inconvenient for most patients and increases the likelihood that doses will be forgotten or skipped.

Low propensity to participate in drug-drug interactions. Some surveys have shown that up to 30% of patients may be coprescribed an antidepressant that interacts with cytochrome P450 enzymes and other prescribed medications.[29] The effects on treatment-associated costs in these populations have not been quantified. A too frequently ignored finding in drug interaction studies is that pharma-

cokinetic interactions do not necessarily translate into clinically significant pharmacodynamic effects. The significance of a drug interaction depends on the order of drug coprescribing and numerous other drug and patient variables.

In the 21st century, antidepressants will be developed that are devoid of or have only minimal effects on inducing or inhibiting cytochrome P450 enzymes. In preclinical studies, new chemical entities are routinely screened for their actions as substrates and/or inhibitors on a variety of enzymes using in vitro preparations. Such studies make it possible to exclude from further development those molecules likely to participate in metabolic drug interactions. However, these in vitro preparations are not perfect. The ability of a new drug to induce hepatic enzymes as a mechanism for participating in drug interactions usually goes undetected without animal or human testing.

CONCLUSION

Development of new antidepressants can be expected to continue at a rapid pace. Perhaps the most difficult challenge to the biomedical industry is to develop drugs with greater degrees of efficacy and more rapid onset of therapeutic effects. In this regard, new data involving the pathophysiology of depression and new molecules with novel mechanisms of action are addressing these unmet needs. Side effect profiles continue to improve, and death from a pure overdose is rare with the newer antidepressants. Clinical trials are beginning to emphasize issues of quality of life as ways to further evaluate the effectiveness of drugs in clinical trials. Pharmacologic screening allows selection of drugs that have the most desirable pharmacokinetic characteristics and low drug interaction potential for development. While no ideal antidepressant exists at the beginning of the 21st century, the direction for development is clear.

Drug names: amitriptyline (Elavil and others), buspirone (BuSpar), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), reboxetine (Vestra), selegiline (Eldepryl), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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