Antidepressants

Alan Frazer, Ph.D.

This review covers the chemical structures, efficacy, side effects, toxicity, and mechanisms of action of various classes of antidepressants: tricyclic antidepressants, monoamine oxidase inhibitors, and second generation antidepressants including the serotonin selective reuptake inhibitors, and novel drugs such as mirtazapine, nefazodone, and venlafaxine.

(J Clin Psychiatry 1997;58[suppl 6]:9–25)

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

The pharmacologic treatment of patients with major depressive disorders can justifiably be viewed as a success story in neuropsychopharmacology. Treatment of such patients with antidepressant drugs causes clinically significant improvement in 65% to 75% of patients and essentially complete recovery in 40% to 50% of patients. There is no doubt that such improvement is drug related, as these percentages are consistently higher than those achieved in patients treated with placebo. Further, the degree of improvement produced by antidepressant drugs is comparable to that achieved by drugs or surgical procedures for non-psychiatric indications.[1] Of course, there remain important drawbacks to the use of these drugs, chief among them being: (1) the 25% to 35% of patients who show minimal improvement; (2) the duration of time (weeks to months) it takes for maximal improvement to occur; (3) side effects; and (4) toxicity.

With the marketing of many newer antidepressant drugs in the United States in the last 10 years, the side effect profile and toxicity of antidepressant drugs has improved considerably. The coalescence of basic and clinical research clearly identified pharmacologic actions of antidepressant drugs that contributed to side effects but not to efficacy.[2] This led to the development of drugs that lacked such pharmacologic properties. Although the newer drugs have their own side effect profiles, in general, they are better tolerated by patients than the original antidepressants, and there is much less toxicity (i.e., serious sequelae including death from overdosage) seen with the newer drugs.

There were two types of original, or first generation, antidepressants: tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The newer drugs are a heterogeneous group. Two of them, amoxapine and maprotiline, are quite similar pharmacologically (if not structurally) to secondary amine TCAs such as desipramine and nortriptyline. Another group of newer drugs shares the common pharmacologic action of selectively blocking the reuptake of 5-hydroxytryptamine (5-HT; serotonin) in vivo and, consequently, have been named serotonin selective reuptake inhibitors (SSRIs). Other newer drugs (e.g., bupropion, nefazodone, trazodone, venlafaxine, and mirtazapine) have a pharmacologic profile distinct from each other as well as the other types of antidepressant drugs. They comprise, therefore, a truly heterogeneous group of atypical antidepressants.

This article will broadly review the chemical structures, efficacy, side effects, toxicity, and mechanisms of action of these drugs. Subsequent articles will cover some of these specific issues in greater detail. Often in reviews of this type, these topics are discussed separately for TCAs, MAOIs, SSRIs, and other atypical antidepressant drugs. However, issues related to efficacy are, in general, similar for all types of antidepressant drugs, and side effect profiles are not necessarily distinguishable by these categories. Consequently, in this paper, the parameters mentioned above will be reviewed together for the different types of antidepressant drugs.

CHEMICAL STRUCTURES

The structures of the different classes of antidepressant drugs are shown in Figures 1–4. As is evident in Figure 1, the trivial name tricyclic antidepressant stems from all these drugs having a three-ring molecular core. Tertiary amine tricyclic antidepressants are demethylated in vivo

From the Department of Pharmacology, The University of Texas Health Science Center at San Antonio and the Audie Murphy Memorial Veterans Administration Hospital, San Antonio, Tex.

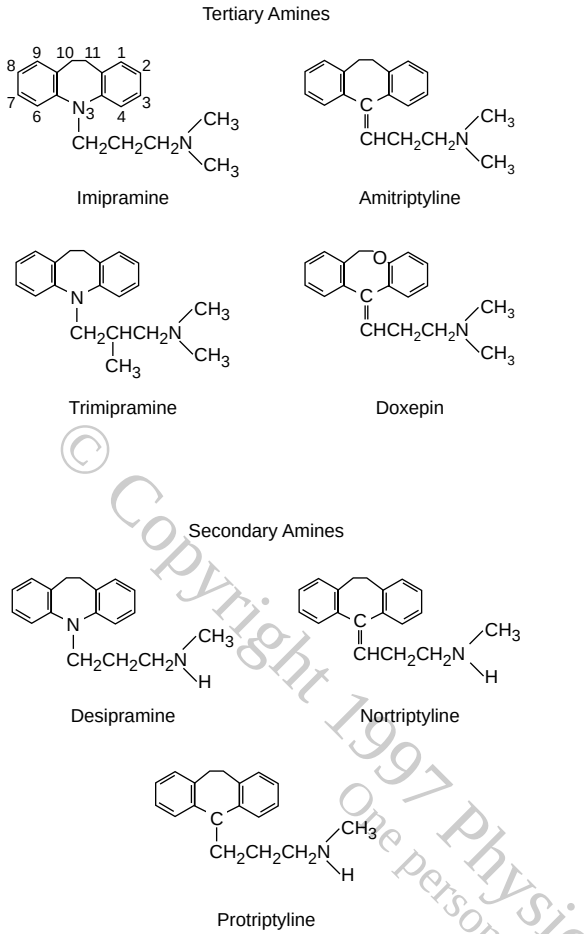
Supported in part from funds from the Department of Veterans Affairs and USPHS grant MH 29094.

Presented at the symposium "Advances in Antidepressant Pharmacotherapy," February 2, 1996, New Orleans, La., supported by an educational grant from Organon Inc.

Portions of this review have previously appeared in the Journal of Clinical Psychopharmacology.

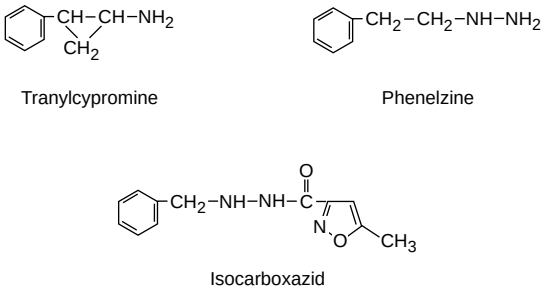
Reprint requests to: Alan Frazer, Ph.D., Department of Pharmacology, University of Texas, Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7764.

Figure 1. The Structure of Tricyclic Antidepressants*



*All these drugs have a three-ring (tricyclic) molecular core.

Figure 2. The Structures of Monoamine Oxidase Inhibitors*



*Isocarboxazid and phenelzine are hydrazine (NH_2NH_2) derivatives.

to their corresponding secondary amine derivatives, e.g., imipramine to desipramine, amitriptyline to nortriptyline.[3] As there are some differences in the pharmacologic profile of tertiary amine and secondary amine TCAs (see above), differences in the extent of such conversions in particular patients might contribute to interindividual variability in, for example, the side effect profile that they produce.

The structures of three MAOIs currently in use in the United States are shown in Figure 2. Isocarboxazid and phenelzine are derivatives of hydrazine (NH_2NH_2). Tranylcypromine, by contrast, is related structurally to amphetamine, and it does have stimulant properties. These MAOIs are mechanism-based irreversible inhibitors of the enzyme. In a mechanism-based reaction, a relatively inert substrate (in this case, these drugs) is converted by a normal enzyme reaction to a highly reactive intermediate that inactivates the enzyme without prior release from the active site.[4] Since all these MAOIs bind to the enzyme essentially irreversibly, inactivation of monoamine oxidase persists even after the drugs are metabolized and removed from the body. Recovery of MAO activity requires the synthesis of new protein, and it can take several weeks for the activity of MAO to return to normal after stopping administration of an MAOI.

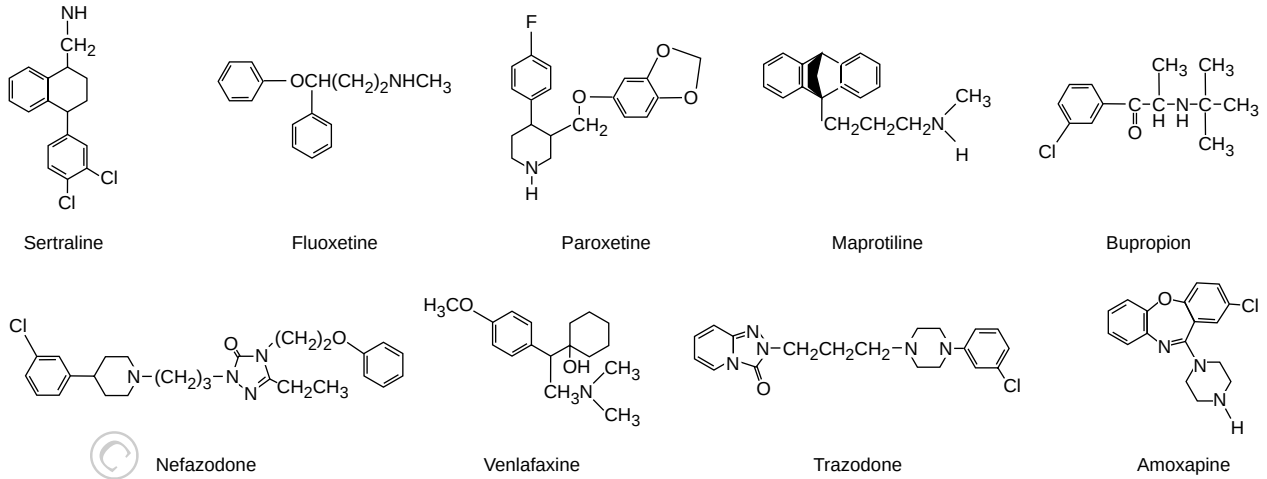
MAO is located in the outer membrane of the mitochondria. In order for a net transporter-induced reuptake of monoamines to occur from the synapse back into the nerve, MAO has to metabolize cytoplasmic amines newly taken up or those that diffuse to keep the concentration of free monoamine in the cytoplasm low. This facilitates inward-directed transporter activity, i.e., reuptake.[5] Inhibition of MAO, then, is associated with an increase of cytosolic monoamines in the neuron terminal. It is still not completely clear how inhibition of intracellularly located MAO affects the concentration of monoamines in the extracellular space.

Three SSRIs are shown in Figure 3: fluoxetine, paroxetine, and sertraline. Fluvoxamine should also be considered with this group, and its pharmacologic profile is presented in this chapter. It is an SSRI; although marketed in this country for the treatment of obsessive-compulsive disorder, it has clearly been demonstrated to be an antidepressant in other countries.[6]

The structures of amoxapine and maprotiline are shown in Figure 3 also. Their pharmacologic profile is, in general, similar to that of secondary amine TCAs, i.e., they block relatively selectively the reuptake of norepinephrine (NE) in comparison to 5-HT (see Table 1) and have comparable potency to the TCAs for blocking H_1 histamine (see Figure 5) or α_1-adrenergic receptors (see Figure 6). The remaining four drugs shown in Figure 3—bupropion, nefazodone, trazodone, and venlafaxine—have pharmacologic profiles distinct from the other antidepressant drugs. In general, they are comparable to the SSRIs in their side effect profile and tolerability by patients. However, bupropion, nefazodone, and trazodone are very weak inhibitors of the uptake of either NE or 5-HT (see Table 1). Venlafaxine, by contrast, does inhibit the uptake of both 5-HT and NE (see Table 1). Finally, the structure of a novel antidepressant, mirtazapine, is shown in Figure 4. Mirtazapine is very similar structurally to mianserin, an antidepressant widely used in Europe. As might be ex-

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

Figure 3. Second Generation Drugs Currently Marketed as Antidepressants in the United States*



*Fluoxetine, paroxetine, and sertraline are serotonin selective reuptake inhibitors (SSRIs). Amoxapine and maprotiline are selective norepinephrine reuptake inhibitors.

Table 1. Potency of Antidepressants to Block Monoamine Reuptake*

Drugs	IC_{50} Values (nM) Norepinephrine	5-HT
TCAs		
Amitriptyline	25	100
Desipramine	2	300
Doxepin	150	2000
Imipramine	25	50
Nortriptyline	6	200
Protriptyline	10	250
Trimipramine	5000	10,000
Second generation		
Amoxapine	25	600
Bupropion	2500	15,000
Maprotiline	40	20,000
Mirtazapine	2000	5000
Nefazodone	600	150
Trazodone	20,000	750
Venlafaxine	300	50
SSRIs		
Fluoxetine	200	15
Fluvoxamine	500	5
Paroxetine	70	1
Sertraline	300	4

*Data from multiple sources in the literature, e.g., references 7–9. Some values have been adjusted to reflect not only the absolute potency of the drug in blocking the reuptake of norepinephrine or 5-HT but also their relative potencies in relationship to each other. The lower the IC_{50} value, the more potent the drug. For example, desipramine is about 150-fold more potent as an inhibitor of norepinephrine reuptake than 5-HT reuptake. Paroxetine, on the other hand, inhibits the reuptake of 5-HT about 70-fold more potently than the reuptake of norepinephrine.

pected from such structural similarity, the pharmacologic profile of these two drugs shows a degree of correspondence. However, some of the modest quantitative differences that do exist between these drugs (e.g., affinities for α_1-adrenoceptors) do appear to have a large impact on certain responses that they elicit (see below).

Figure 4. Structure of the Novel Antidepressant Mirtazapine*

*Mirtazapine is a derivative of mianserin, whose structure is shown for comparative purposes.

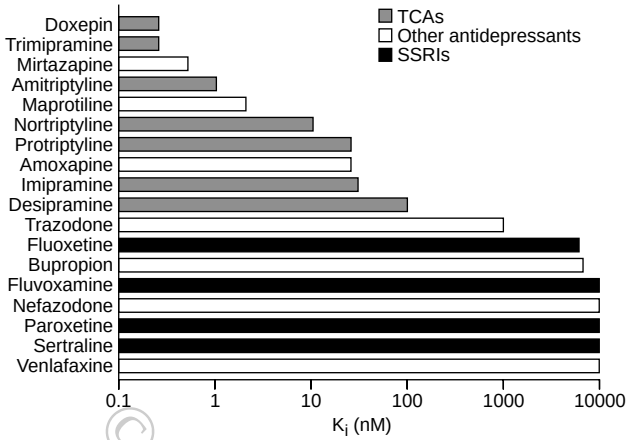
EFFICACY

The prototypical TCA is imipramine, the efficacy of which was originally reported in 1958 by Kuhn.[12] As a group, TCAs may still be the most commonly prescribed pharmacotherapy by psychiatrists for depression.[13] The overall efficacy of these drugs is comparable, causing clinically significant improvement in a much greater percentage of patients than that seen with placebo.[14,15] In direct comparison with placebo, the TCAs were statistically superior in about three quarters of the trials.[16] Not all depressed patients respond equally well to TCAs. For example, only about 50% of patients with "atypical" depression—those who have symptoms of mood reactivity, rejection sensitivity, leaden paralysis, overeating, and oversleeping—respond well to imipramine.[17] Also, psychotic depressed patients have a lower response rate to TCAs than nonpsychotic patients. However, whether this is due to psychosis or to the fact that psychotic depressed patients tend to be more severely ill than nonpsychotic depressed patients is still unclear.[18]

At about the time that imipramine was reported to be efficacious, the MAOI iproniazid was also found to be an antidepressant.[19,20] The overall efficacy of MAOIs in ma-

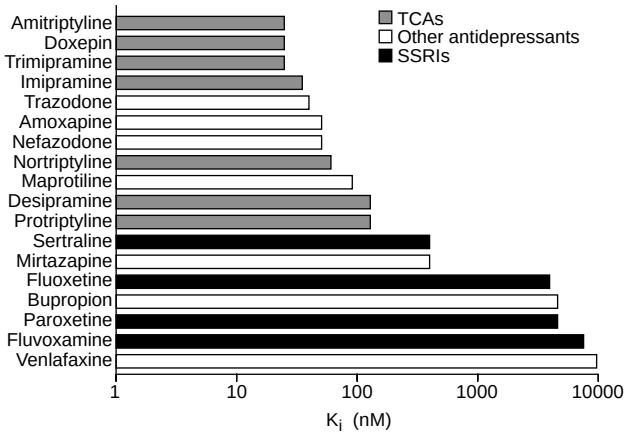
© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

Figure 5. Potency of Antidepressants to Block H_1 Histamine Receptors*



*Data from references 7,10, and 11. Some values may have been adjusted to reflect not only the absolute potency of the drug in blocking H_1 histamine receptors but also their relative potencies in relationship to each other. The relationship between K_i values (the concentration of drug needed to occupy 50% of the receptors) and IC_{50} values is given by the equation $K_i = IC_{50}/1 + L/K_D$, where L is the concentration of radioligand used in the experiment and K_D is the affinity of the radioligand for the receptor. The more potent the drug, the lower the K_i value.

Figure 6. Potency of Antidepressants to Block α_1-Adrenergic Receptors*



*Data from references 7,10, and 11. Some values may have been adjusted to reflect not only the absolute potency of the drug in blocking α_1-adrenergic receptors but also their relative potencies in relationship to each other. The relationship between K_i values (the concentration of drug needed to occupy 50% of the receptors) and IC_{50} values is given by the equation $K_i = IC_{50}/1 + L/K_D$, where L is the concentration of radioligand used in the experiment and K_D is the affinity of the radioligand for the receptor. The more potent the drug, the lower the K_i value.

jor depression seems comparable to that of the TCAs, although more severely depressed inpatients may not respond as well to MAOIs as to TCAs.[16] Whether MAOIs are as effective in patients with typical depression as they are in patients with atypical depression has been controversial.[21,22] Patients with typical depression would be those who meet current standard diagnostic criteria or, historically, those described by Kuhn as being good responders to TCAs. By contrast, a variety of symptom clusters have been used to describe atypical depression; these often include overeating, oversleeping, mood reactivity, and rejection sensitivity, with the symptomatology becoming worse, rather than better, in the evening. Murphy et al.[23] reviewed data on the efficacy of MAOIs and concluded that they were "as effective as the tricyclics in all recent controlled studies of typical populations of depressed patients meeting current diagnostic criteria as in those patients with so-called atypical depression." A more recent review[21] reached the same conclusion, especially when the MAOIs are used in larger doses or in such patients who initially fail to respond to TCAs.

On the other hand, Quitkin, Klein, and their associates have provided convincing evidence of a subgroup of patients with depression that is preferentially responsive to phenelzine.[17,24,25] These depressed patients were defined as being atypical, in that they were mood reactive and had at least two of the following symptoms: hyperphagia, hypersomnolence, rejection sensitivity, or leaden paralysis (i.e., severe fatigue causing a marked decrease in energy or heaviness of limbs). In this group of depressed patients, both phenelzine and imipramine were superior to placebo, which produced a 25% response rate. The response rate to phenelzine (79%), however, was markedly superior to that of imipramine (52%). The superior response rate to phenelzine was not confined to atypical patients with a history of panic attacks. Tranylcypromine also seems to be more effective in such patients than TCAs.[21] Inclusion of this subgroup in clinical trials of TCA nonresponders may account, in large measure, for the claims that TCA nonresponders respond well to MAOIs.[26–28]

There are at least two isoenzymes of MAO, referred to as type A and type B. Evidence for the existence of these isoenzymes was based initially on differing substrate specificities and differential sensitivity to inhibitors of MAO. Clorgyline is a selective inhibitor of the type A form, whereas deprenyl is selective for the type B isoenzyme. Definitive proof that these two forms of MAO exist is now available with the cloning of cDNAs encoding subunits of each isoenzyme from human liver.[29] The irreversible inhibitors of MAO shown in Figure 2 are nonselective, i.e., they inhibit both isoenzymes. However, it is the inhibition of type A monoamine oxidase that is preferentially associated with antidepressant activity.[23,30]

The efficacy of the newer drugs has been compared with that of TCAs or placebo. Their efficacy is superior to that of placebo and comparable to that of TCAs, but no better. They have not consistently been shown to produce more improvement than TCAs in depressive symptomatology, to improve a greater percentage of patients, or to cause more rapid improvement. Workman and Short[31]

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

conducted a meta-analysis of data from clinical trials in which either bupropion, fluoxetine, or trazodone was compared with imipramine. All the studies were placebo controlled, and their results were published in seven major psychiatric journals between 1980 and 1990. A total of 2090 patients were included in these studies. All the drugs were more efficacious than placebo, but there was no difference among the four drugs in their effect size in comparison with that of placebo. In other words, the newer drugs had efficacy comparable to that of the "gold standard" TCA, imipramine. Amoxapine[32] and maprotiline[33] also exhibit efficacy equivalent to that of the TCAs. Interestingly, bupropion has been found to be effective in nonresponders to TCAs.[34]

Rickels and Schweizer[35] reviewed the efficacy of SSRIs and concluded that they were not more efficacious nor faster acting than TCAs but were comparable in efficacy. The use of other statistical approaches yielded a similar conclusion.[36] Others who reviewed specific SSRIs reached the same conclusion.[37–39] In general, substantial improvement is obtained in about twice as many patients with the SSRIs as with placebo and in a percentage comparable to that with TCAs. Fluvoxamine has been found to be effective in both inpatients and outpatients, whereas the efficacy of the other SSRIs has been evaluated primarily just in outpatients.[36] There are data from which it has been inferred that SSRIs may be more efficacious in severe depression than TCAs or in depressives with prominent anxiety symptoms.[40] Such conclusions must be viewed with caution as they come from retrospective meta-analyses of databases. Properly designed prospective studies will be needed to validate or refute such claims.

The efficacy of venlafaxine has also been evaluated in outpatients as well as inpatients. Venlafaxine was effective in treating both severely depressed inpatients with melancholia[41] and outpatients with major depression.[42] Results from outpatient studies indicate that venlafaxine has efficacy comparable to that of standard therapies such as imipramine or trazodone.[42,43] In two studies of depressed, hospitalized patients with melancholia, treatment with venlafaxine was shown to be superior to either placebo or fluoxetine treatment.[41]

Not surprisingly, both nefazodone[44] and mirtazapine[45] have been reported to have efficacy superior to placebo and comparable to that of standard antidepressant drugs such as amitriptyline or imipramine. Mirtazapine is also efficacious both in inpatients and outpatients.[46,47] Recently, the efficacy of mirtazapine was compared with that of trazodone in a study of 200 hospitalized depressed patients.[48] After 6 weeks of treatment, the mirtazapine-treated patients had a significantly greater response rate and a significantly greater reduction in symptomatology in comparison to that of the trazodone-treated patients, as assessed by the Hamilton Rating Scale for Depression (HAM-D).

An important limitation of all antidepressants is the time it takes for their maximal therapeutic effects to occur. Essentially all studies of the efficacy of antidepressant drugs demonstrate this time to be 4–6 weeks or longer. A more rapid maximal effect would be of obvious benefit in terms of patient suffering and the potential for suicide. An issue related to time for maximal improvement is the rate of onset of antidepressant action. Clinical lore holds that there is a lag phase of 2 weeks or longer before drug-induced beneficial effects become evident. This has been interpreted as indicating that it takes antidepressant drugs 2 or more weeks to begin to work. Clarification of this has considerable importance for several reasons. First, if it is really true that drug-responsive patients show no evident improvement early in treatment, then there is little rationale for altering treatment early on for apparently nonresponding patients. Alternatively, if early improvement predicts subsequent antidepressant response, then the absence of this would warrant stopping treatment with a particular drug and doing whatever is next deemed appropriate for the nonresponsive patient. Second, if there is really little-to-no drug-related improvement early in treatment, then later-developing pharmacologic effects of antidepressant drugs may be more relevant for efficacy than acute effects.

The idea of delayed onset of efficacy produced an entire field of investigation, namely the study of slowly developing, adaptive effects produced by antidepressant drugs on central monoamine systems.[49,50] Such studies have contributed greatly to our understanding of regulatory processes in these neuronal systems, processes that have physiologic, and perhaps even pathophysiologic, importance. For example, repeated, but not acute, administration of many, but not all, types of antidepressant drugs reduces responses elicited by activation of central β adrenoceptors, with this effect accompanied by a decrease in density or "down-regulation" of these receptors.[51–54] Another example of this type of adaptive process concerns the firing rate of serotonergic soma in the raphe nuclei. Very shortly after the administration of many antidepressant drugs, these soma decrease their rate of firing.[55] In spite of continued administration of antidepressant drugs, the firing rate of these soma returns to predrug levels after about 2 to 3 weeks.[56] Because these and other adaptive changes induced by antidepressant drugs take time to develop, some investigators have speculated that it is these adaptive effects that are crucial for clinical efficacy.[57,58]

In reality, though, the question of when antidepressant drugs begin improving depressive symptomatology is very difficult to answer and has not been addressed adequately. Several factors contribute to the difficulty of answering this question. One confounding factor is that depressed patients do respond, at least partially, to placebo, and onset of drug action has been defined as the time when improvement produced by drug is statistically greater than

© Current Medicine Physicians Postgraduate Press, Inc.
For personal use only. May be copied.

that caused by placebo. Certainly, such a separation may require several weeks or more of treatment.[59] As Burke and Preskorn[60] have pointed out, this approach does not truly measure onset of action but rather the ability to detect an average difference between drug and placebo efficacy. The placebo-induced drop in average depression severity scores soon after treatment is initiated limits early detection of drug-specific effects. Further, the presentation of the results of these types of efficacy studies almost always combines the results of drug-responsive and nonresponsive patients. It would seem important to examine the rate of drug response only in patients who have met criteria for good or excellent response after a suitable period of time. Inclusion of nonresponders would decrease the apparent rate of drug response.

Another issue to consider is whether the rating scales used in most clinical trials are sufficiently sensitive to detect subtle, but important, early changes in depressive symptomatology. Typical global rating scales used in clinical drug trials, such as the HAM-D,[61] do not measure specific aspects of the syndrome with great sensitivity. Indeed, it was for this reason that the Montgomery-Asberg Depression Rating Scale[62] was developed to be sensitive to drug-induced change. Finally, dose is often raised slowly, such that adequate therapeutic doses may not be achieved early in treatment. Some authors have speculated that the apparent delay in improvement may be related to the time needed to achieve a therapeutic steady-state concentration of drug in plasma.[63]

In view of this, it is not surprising that early drug-induced behavioral improvement has been difficult to detect. To do this properly, Prien et al.[64] stated that such studies require: (1) predetermined criteria for the change considered clinically significant; (2) frequent clinical assessments; (3) appropriately aggressive dosage schedules; (4) use of a placebo to control for nonspecific responses; (5) adequate sample size to detect a true early difference between treatments. Such a study is designed quite differently from a typical drug efficacy study. Indeed, there were essentially no studies reviewed by Prien et al.[64] that had all these features.

Interestingly, some of the newer antidepressant drugs have a side effect profile that allows a more rapid titration to maximal dosage than could be done with TCAs. In some cases when this was done, early improvement was detected. For example, depressed patients whose dosage of venlafaxine was rapidly raised to above 200 mg daily within the first week of treatment showed improvement in depression that was significantly greater than that due to placebo as early as Week 1.[65] Treatment with fluoxetine is usually initiated at the dose that will be used throughout the drug trial, although the long half-life of this drug and its principal metabolite means that steady-state concentration of active drug in plasma will not occur for many weeks after treatment has begun.[40] Nevertheless, a meta-analysis of patients treated with fluoxetine or placebo showed statistically greater global improvement caused by fluoxetine within 1 week of treatment initiation.[66] Such data are of interest as the studies were not necessarily designed to detect a rapid onset of action.

Another factor of relevance for the issue of onset of action is that major depressive disorder is thought to be a syndrome, comprised of behavioral, cognitive, and somatic components. These components may change at different rates during the course of treatment,[67] implying that there is no single onset of action, but rather multiple "onsets." There have been several studies that have attempted to examine the "pattern of recovery" from depression. None, though, were truly designed to address the issue of onset, according to the criteria proposed by Prien et al.[64] Small et al.[68] reported data from a multicenter study evaluating the efficacy of trazodone, imipramine, and placebo. Treatment continued for 4 weeks and the patients were classified categorically as responders or nonresponders. Data were presented for five individual factors from the HAM-D. When the data from all patients were analyzed, the two active drugs were nearly indistinguishable in causing improvement of the five factors, but they were uniformly better than placebo. In the responders, the profiles of response were similar for both active treatments and the placebo group. It was concluded that recovery from depression by any therapeutic intervention (including placebo) is similar in terms of the kinds of improvement observed during the first 4 weeks of treatment. The data also showed that the most dramatic improvement is seen in the first week of treatment, again irrespective of treatment modality. They concluded that if minimal change in behavior is observed after the first week of therapy, the patient is likely to be a nonresponder at endpoint.

More recently, Stassen et al.[69] reached similar conclusions from their meta-analysis of a multicenter efficacy study of amitriptyline, oxaprotiline, and placebo. Response was considered to be at least a 50% reduction on the HAM-D score from baseline. Specific types of behavioral changes were not presented. Similar to the results of Small et al.,[68] the time course of global improvement among responders was identical in all three treatment groups.

Katz et al.[70] studied a group of severely depressed inpatients whose dosage of either amitriptyline or imipramine was raised rapidly (within 1 week) to the maximal amount. They examined the specific components of depression as well as the syndrome as a whole and assessed whether initial patterns of behavioral improvement could predict eventual therapeutic response. After 4 weeks of treatment, patients were placed into nonresponder or responder groups based on predetermined criteria. After drug therapy was initiated, improvement was found to occur within 1 week in behaviors such as anxiety, hostility, and physical distress in the drug-responsive but not in the nonrespon-

© Current Medical Physicians Postgraduate Press, Inc.
One personal copy may be printed

sive patients. It was concluded that if drug treatment of depression is going to be effective, then positive changes in behavior will occur within the first week of treatment. This conclusion should be viewed with caution, since this study did not include a group of patients maintained on placebo.

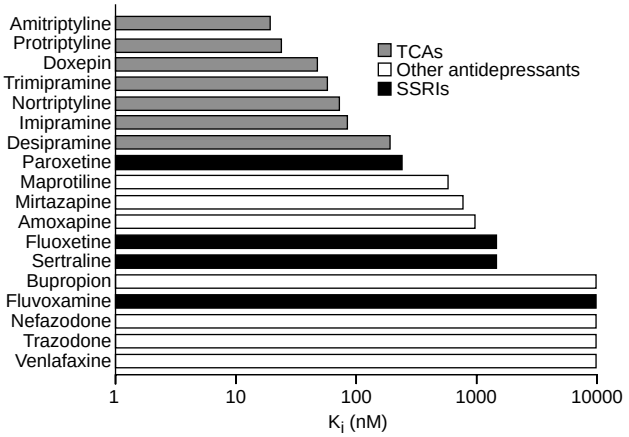
At the present time, then, it can be concluded with certainty that maximal clinical improvement with all types of antidepressant drugs takes weeks, if not months, to occur. Less certain is whether there is truly a delay in the initiation of behavioral improvement caused by antidepressant drugs. It is worth noting that the concept of a lag period does not agree with Kuhn's[12] original observations on the rate of response to imipramine. Further research to clarify the initial pattern(s) of drug-induced behavioral improvement is warranted.

SIDE EFFECTS

It is now clear that the side effects produced by many of the antidepressant drugs are a consequence of their ability to block muscarinic cholinergic receptors, H_1 histamine receptors, and α_1-adrenergic receptors.[2] The affinity values (K_i) of the various types of antidepressant drugs for these receptors are shown in Figures 5–7. The lower the K_i values, the more potently the antidepressant blocks the receptor. Because of the very wide range of K_i values for the antidepressant drugs, the abscissa in these figures is presented in logarithmic units.

Blockade of muscarinic cholinergic receptors causes side effects that occur quite frequently—dry mouth, blurred vision, constipation, urinary retention. Sinus tachycardia and short-term memory impairment can also be due to muscarinic cholinergic blockade. As shown in Figure 7, the TCAs as a group are clearly more potent at blocking these receptors than other types of antidepressant drugs, and they all can cause these types of side effects. Consistent with their high potency at muscarinic receptors, amitriptyline and protriptyline tend to produce anticholinergic side effects with the highest frequency.[71] MAOIs have little affinity for muscarinic cholinergic receptors (data not shown) and tend not to cause these side effects. Although amoxapine and maprotiline are somewhat less potent at muscarinic receptors than TCAs, they do produce anticholinergic side effects, perhaps to an extent comparable to that of the TCAs.[32] Even though the SSRI paroxetine has reasonable affinity for muscarinic receptors, it produces less marked anticholinergic effects than do the TCAs.[37,72] This may be because it is given in lower dosage than many TCAs and, in general, achieves lower steady-state plasma concentrations than most of the TCAs.[38] For similar reasons, mirtazapine also does not seem to cause the full spectrum of anticholinergic side effects.[73] Because of their low potency at blocking muscarinic receptors, other SSRIs and atypical antidepressant drugs cause essentially no more anticholinergic side effects than placebo.

Figure 7. Potency of Antidepressants to Block Muscarinic Cholinergic Receptors*



*Data from references 7, 10, and 11. Some values may have been adjusted to reflect not only the absolute potency of the drug in blocking muscarinic cholinergic receptors but also their relative potencies in relationship to each other. The relationship between K_i values (the concentration of drug needed to occupy 50% of the receptors) and IC_{50} values is given by the equation $K_i = IC_{50}/1 + L/K_D$, where L is the concentration of radioligand used in the experiment and K_D is the affinity of the radioligand for the receptor. The more potent the drug, the lower the K_i value.

Blockade of H_1 histamine receptors causes sedation and drowsiness, and perhaps contributes to weight gain as well. As evident in Figure 5, many antidepressant drugs show very high affinity for these receptors, even more so than their affinities for muscarinic receptors. H_1 histamine receptor blockade can also lead to the potentiation of the effects of other central nervous system depressants. Among the TCAs, sedation and drowsiness are commonly seen with doxepin, trimipramine, amitriptyline, and imipramine. Interestingly, the secondary amine TCAs—desipramine, nortriptyline, and protriptyline—are less sedating than the other TCAs. The high potency of amoxapine and maprotiline at H_1 histamine receptors probably accounts for their causing sedation similar to that of amitriptyline or imipramine. Even though both trazodone and nefazodone are weakly potent at H_1 histamine receptors, they are quite sedative. This may be due in part to their high affinity for α_1-adrenoceptors (see Figure 6). However, it may also be a consequence of the fact that the steady-state plasma concentrations of these two antidepressants is much higher than that of other antidepressant drugs, often reaching the micromolar range.[74–76] Thus, at therapeutic doses, concentrations of either trazodone or nefazodone in plasma may be sufficient to cause some blockade of H_1 histamine receptors. Given its high affinity for H_1 histamine receptors, it is not surprising that mirtazapine also causes drowsiness and sedation.[73] Little sedation or drowsiness is caused by the SSRIs, bupropion, venlafaxine, or the MAOIs.

© Copyright Physicians Postgraduate Press, Inc.
One personal copy may be printed

Orthostatic hypotension and perhaps sedation is associated with blockade of α_1-adrenoceptors. The sedative effect may be a consequence of NE acting centrally to increase arousal or vigilance.[77] Presumably due to their relative high affinity at α_1-adrenoceptors (see Figure 6), all TCAs can cause orthostatic hypotension. This can occur in as many as 20% of patients treated with TCAs; it is particularly a problem in elderly patients.[71] Since the hypotension is not consistently related to dose,[71] it can occur anytime during treatment. Among the TCAs, postural hypotension is observed least frequently with nortriptyline.[78] Both trazodone and nefazodone are potent at blocking α_1-adrenoceptors[79]; for unknown reasons, nefazodone seems to cause less orthostatic hypotension than trazodone. Amoxapine and maprotiline also produce this effect. None of the other antidepressant drugs potently block this receptor, and they produce little, if any, orthostatic hypotension. MAOIs also have comparable potential to the TCAs for causing orthostatic hypotension, even though they do not cause this effect by blocking α_1-adrenoceptors.

Interestingly, venlafaxine can cause a dose-related increase in blood pressure in some patients. The likelihood of patients receiving 100 mg or less of venlafaxine having a sustained elevation of blood pressure was no greater than that of patients receiving placebo.[80] However, for patients receiving between 101–300 mg of venlafaxine daily, the percentage having a sustained blood pressure elevation was 3% to 4% higher than that of the placebo-treated patients. About half of the venlafaxine-treated patients defined as having a sustained blood pressure elevation no longer met the criteria for this categorization when blood pressure measurements were taken subsequently, even though the patients continued to receive venlafaxine.

The TCAs affect the myocardium because of a combination of anticholinergic activity, inhibition of amine reuptake, and direct depressant effects. These effects are most commonly manifested as a mild tachycardia. However, conduction disturbances and electrocardiographic (ECG) changes can occur. Changes in the ECG include prolongation of PR, QRS, or QT intervals or flattening or inversion of T waves due to a slowing of both atrial and ventricular depolarization. The slowing of depolarization can lead to atrioventricular or bundle-branch block or to premature ventricular contractions. These side effects are cause for concern even though they occur much more commonly in patients with preexisting cardiac problems.[81] With therapeutic doses of TCAs, abnormalities of cardiac conduction occur in less than 5% of patients and most are not clinically significant.[78]

Amoxapine and maprotiline may have somewhat less of an effect on cardiac conduction and the ECG than the TCAs do.[32,33] The SSRIs and other atypical antidepressants have virtually no effect on the conduction system of the heart and produce much less effect on the ECG than the TCAs. The MAOIs also do not cause conduction disturbances or have important direct cardiac effects.

TCAs cause a number of other side effects less frequently than those enumerated above. An important side effect is weight gain, in part because it reduces the likelihood that patients will continue to take their medication.[82] Amitriptyline appears most likely to cause significant weight gain, whereas desipramine and nortriptyline are the least likely.[83] Weight gain also occurs in patients treated with MAOIs, particularly with phenelzine.[82] Most SSRIs have an anorectic effect and do not cause any clinically significant weight gain. Paroxetine appears to be unique among SSRIs in having no clinically significant anorectic effect,[37] and weight gain has been reported in patients being treated with paroxetine over time.[38] Bupropion also does not cause the weight gain associated with the older antidepressant drugs.[84,85] Venlafaxine can cause weight loss which is often transient; patients treated with this drug in clinical trials show a modest decrease in weight during the first 5 months of treatment but an increase of about 5 lb after 8 months.[80] Perhaps due to its potent antihistaminic effect, treatment with mirtazapine is also associated with modest weight gain.[73] Trazodone also can cause weight gain, but it is too early to know the effect of nefazodone on weight gain.

Since TCAs may lower the seizure threshold, they are potentially epileptogenic. It has been estimated that TCA-induced seizures occur in 0.1% to 0.5% of patients.[86] Seizure activity appears to be related to dose and the rate of dose escalation, and it usually occurs early in treatment. Similar to the TCAs, a number of the newer drugs lower the seizure threshold and can induce seizures. Induction of seizures is particularly pronounced with maprotiline and bupropion, especially in patients receiving high doses (e.g., > 225 mg/day of maprotiline or > 450 mg/day of bupropion).[86] By contrast, the incidence of seizures is very low with trazodone, nefazodone, and mirtazapine, and the incidence with SSRIs is lower than that with TCAs.[37,38,73,86–88] The incidence of seizures in patients treated with venlafaxine (0.26%) was somewhat lower than that in patients treated with a reference antidepressant, mostly TCAs (0.38%), during clinical trials.[80] Seizures do not seem to occur in association with MAOIs.[86]

An important CNS side effect of TCAs is their inducing mania or hypomania in patients with bipolar depression or in patients with depression and a strong family history of bipolar disorder.[71] This side effect also occurs in patients treated with MAOIs. There appears to be somewhat less risk of this occurring in patients treated with SSRIs,[72,89] but this may be due to bipolar patients generally being excluded from clinical trials. Further examination of this issue is warranted. There are insufficient data to assess the risk of this effect occurring with other atypical antidepressant drugs (compare, for example, the conclusion of Fogelson et al.[90] regarding the risk of bupro-

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

pion inducing manic episodes with the conclusion of Sachs et al.).[91]

In general, all the newer antidepressant drugs show improved patient tolerability in comparison to the TCAs. As with all drugs, though, there are side effects produced by these newer compounds. There are similarities in the side effect profiles of SSRIs. They all cause nausea (15% to 35% incidence), vomiting, and diarrhea to a considerably greater extent than the TCAs do.[35,38,88] Nausea is the most common side effect of these drugs, and, for most of them, somnolence is relatively frequent also. Both the nausea and somnolence tend to dissipate over time as the drugs continue to be taken. Headache is also a common side effect of this class of drugs and increases in frequency over time. Fluoxetine appears to be distinct among the SSRIs in producing a relatively high incidence of insomnia, nervousness, restlessness, and anxiety.[35] By contrast, fluvoxamine seems to produce agitation and anxiety at a particularly low rate.[88]

Venlafaxine has a side effect profile similar to that of the SSRIs,[42–44] but it does not seem to have the stimulant effect that can occur with fluoxetine. Further, a rapid tolerance develops to the nausea caused by venlafaxine.[80] Bupropion, though, can cause nervousness and insomnia (as well as tremors and palpitations) and has more of a stimulant than a sedative profile.[92] The occurrence of nausea and vomiting in patients treated with either trazodone, nefazodone, or bupropion is, in general, less than that seen in patients treated with SSRIs or venlafaxine.[73,92] Mirtazapine causes a much lower incidence of nausea and vomiting than that seen with either SSRIs or venlafaxine.[45,73]

An antidepressant-induced side effect that is receiving increasing attention is sexual dysfunction.[93,94] Such side effects can include abnormal ejaculation/orgasm, anorgasmia, impotence, decreased libido, dysmenorrhea, and menstrual complaints. Estimates of such side effects are quite variable.[93] Sertraline causes more sexual dysfunction in males than in females.[93] The placebo-adjusted incidence of such side effects for different SSRIs varies widely.[92] It is not clear if there is truly such variability or whether the ascertainment of the incidence of these effects was different in various studies. Venlafaxine also appears to produce sexual dysfunction, also more in males than in females.[92] There appears to be little impairment of sexual functioning in patients treated with bupropion,[92,93,95] and perhaps with nefazodone as well. To date, the only sexual dysfunction symptom seen with mirtazapine is decreased libido, and this occurred in a low percentage of patients.[73] It is interesting that there were no reports of priapism during the clinical trials of nefazodone, since it is structurally similar to trazodone, which is well known to cause this effect.[96,97] Given the number of patients studied in such trials and the low incidence with which priapism occurs with trazodone, careful postmarketing surveillance for this side effect with nefazodone will be necessary before it can be concluded that it does not occur. Finally, it should be noted that both TCAs and MAOIs can also cause sexual dysfunction including loss of libido, impaired erectile function, impaired or painful ejaculation, impotence, and anorgasmia. In fact, it was recently concluded that the incidence of sexual dysfunction was highest with TCAs and MAOIs, intermediate with SSRIs and venlafaxine, and lowest with bupropion and trazodone.[93]

Among all antidepressant drugs, amoxapine has the greatest potential for producing neuroleptic-like side effects, due either to its high affinity or that of one of its metabolites for D_2 dopamine receptors. Treatment with amoxapine can cause the movement and neuroendocrine disorders associated with antipsychotic treatments, but the incidence of these effects with amoxapine seems much lower than that seen with typical neuroleptics.[98]

TOXICITY

TCAs can be toxic. TCA-induced toxicity of the CNS can cause delirium, which is easily recognizable. However, this is preceded by symptoms that may appear as either a worsening of depression or the development of psychosis. The mean incidence of such toxicity is correlated positively with plasma concentrations of the TCAs.

Overdosage of TCAs can cause death. This is of great concern, as depression is the disorder most commonly associated with deliberate self-harm. Suicide by poisoning accounts for about 20% of all suicides, and TCAs are the most commonly used drugs in suicides by poisoning.[99] For every million patients treated with TCAs, 100 to 150 will make a self-poisoning attempt.[100] Overdosage with TCAs can produce coma, seizures, hypertension, ECG abnormalities, and arrhythmias. Death from TCA overdose is primarily due to cardiac arrest.[101] Desipramine may be associated with more deaths per overdosage than other TCAs.[99,102] Although difficult to estimate accurately, a lethal dose of a TCA may be as low as 1200 mg and almost always occurs with doses of 2000 mg or greater.[103] This is no more than 10 to 15 times greater than the standard therapeutic daily dose for most of these drugs.

The most publicized and alarming toxic effect of MAOIs is hypertensive crisis. The high blood pressure may elicit a headache that can be accompanied by sweating, pallor, nausea, and vomiting. More serious and even fatal syndromes can develop, such as intracranial hemorrhage due to the hypertensive crisis.[104] The acute, dramatic increase in blood pressure is not a toxic effect of MAOIs alone but is more properly considered a drug (or food) interaction.[105] For example, the rise of blood pressure may be due to the ingestion of foods containing indirectly acting sympathomimetic amines such as tyramine. Cheese is rich in tyramine, and when the development of hypertension in a patient being treated with an MAOI was traced originally to her ingestion of cheese, the hypertensive crisis was

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

termed the "cheese reaction." Tyramine raises blood pressure by releasing norepinephrine and epinephrine from either sympathetic nerve terminals and/or the adrenal medulla. Normally, tyramine is metabolized by MAO, primarily type A, in the gastrointestinal tract and does not enter the circulation to an appreciable extent. However, if MOA-A is inhibited, then tyramine enters the circulation and releases the greater than normal amounts of catecholamine stored in nerve terminals, causing the hypertensive crisis.[105,106] Among the currently available MAOIs, tranylcypromine seems most likely to cause hypertensive episodes.[105] Patients treated with MAOIs have extensive, complicated dietary restrictions.[107] More recent data on the tyramine content of many foods and beverages[106] indicate that there was little rationale for many of these diets. Rather than the 700 food items prohibited in some diets, it appears that only aged cheese, pickled herrings, concentrated yeast extract, and broad bean pods need to be avoided totally.[105] Equally important, numerous over-the-counter cold and sinus medications contain indirectly acting sympathomimetic amines, and their use should also be avoided by patients treated with MAOIs.

There is another serious drug interaction with MAOIs. Certain drugs used during anesthesia, e.g., pethidine, have caused severe and even fatal responses in patients being treated with MAOIs. Consequently, anesthesiologists have usually required withdrawal of MAOIs for 2 to 3 weeks before surgery performed under anesthesia.[108]

Overdosage with MAOIs alone can cause very serious, even life-threatening, problems. The onset of symptoms usually occurs 6 to 12 hours after ingestion but can be delayed up to 24 hours. Early symptoms include faintness, anxiety, flushing, sweating, headache, tachypnea, tachycardia, and tremor. More serious symptoms include muscular hyperactivity, coma, seizures, profound hypotension, and cardiac arrest.[109] An acute overdosage of 4 to 6 mg/kg body weight can be fatal.[110]

In general, the SSRIs and the other atypical antidepressant drugs (except amoxapine and maprotiline) have a higher therapeutic index than the TCAs do.[103] Overdosage with these drugs does not appear to have the life-threatening consequences associated with TCAs. Deaths have occurred following overdosage with trazodone, although in the great majority of cases, serious adverse effects have not occurred and recoveries were uneventful.[79] Of 28 patients who overdosed with paroxetine, with the largest dose being 850 mg, all achieved full recovery with conservative clinical management. Neither cardiovascular toxicity nor seizure activity was noted.[37] Seven patients who ingested up to 13 times the maximum recommended dose of sertraline recovered completely.[39] As of 1989, there were 58 reports of overdosage with fluvoxamine; 9 patients died, but all of these took multiple medications.

Bupropion also may have a better therapeutic index than TCAs. Five female patients who ingested 900 to 3000 mg of bupropion in single doses did not have any serious adverse effects; there were no cardiac abnormalities or seizures and no impairment of consciousness.[111] A 3-year multicenter, retrospective analysis of bupropion overdosage reported to poison control centers was published recently.[112] There were 58 cases of bupropion ingestion alone and nine cases of bupropion combined with a benzodiazepine. No deaths occurred. Cardiovascular abnormalities were limited primarily to sinus tachycardia. Neurologic toxicity included lethargy and tremors. Seizures occurred in 13 patients.

Compared to the TCAs, venlafaxine appears to present few toxicity problems with overdose. Fourteen patients have taken overdoses of venlafaxine, in some cases what appears to be about 10 times more than the recommended maximum dose. Plasma concentrations more than 30-fold higher than therapeutic levels have been recorded. All patients recovered without sequelae; the most commonly reported symptoms were somnolence and sinus tachycardia. One patient who ingested 2.75 g venlafaxine along with 10 g naproxen and 0.5 mg thyroxine experienced two generalized convulsions, became deeply comatose, and required assisted ventilation before recovering.[80]

Mirtazapine also appears to have less serious sequelae associated with overdose than the TCAs do. During clinical trials with this antidepressant, 10 patients took overdoses of mirtazapine—4 of them took mirtazapine alone in doses up to 5–7 times greater than the usual daily dose. Transient somnolence was the dominant clinical symptom, without any clinically relevant changes in vital signs or the ECG.[73] Further, an elderly patient who took about 20 times the recommended dose of mirtazapine in combination with about 14 times the recommended dose of midazolam recovered without serious adverse effects.[73] She entered a semicomatose state followed by transitory somnolence. Neither respiratory nor cardiovascular functions were compromised, and seizures were not observed.

MECHANISMS OF ACTION

The advent of the newer antidepressant drugs clarifies some issues and raises other ones about mechanism(s) of action of antidepressants. The 30-year-old monoamine hypotheses of depression,[113–116] postulating a functional deficiency of noradrenergic or serotonergic transmission at key sites in the brain, were based in large measure on the acute pharmacologic actions of TCAs and MAOIs. These hypotheses followed the discovery that these antidepressant drugs either blocked the uptake of NE and 5-HT or inhibited the catabolism of these monoamines by monoamine oxidase. As TCAs also had anticholinergic properties, it was speculated that such an action also contributed to their antidepressant activity and, further, that cholinergic hyperactivity contributed to the pathogenesis of depression.[117] Consequently, that most of the newer

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

antidepressant drugs (as well as the traditional MAOIs) have essentially no anticholinergic properties implies that such activity contributes solely to side effects and not efficacy. This is likely to be true also for the H_1 histamine receptor and α_1-adrenergic receptor antagonism produced by many of the antidepressant drugs.[2]

Since none of the TCAs *selectively* blocked the uptake of serotonin in vivo, it was difficult to ascertain what effect, if any, serotonin uptake inhibition contributed to their antidepressant activity. Several theories were proposed in which different behavioral effects were attributed to NE and to 5-HT (e.g., see reference 118). Because of the SSRIs, we now know that drugs with selective effects on either NE or 5-HT can be antidepressants. Further, there seems little evidence to distinguish between the efficacy of these two types of antidepressants or to differentiate among the patients that they help. Whether the initial pattern of behavioral improvement elicited by these two different classes of antidepressant drugs is similar or different needs to be addressed given that maximal improvement with drugs such as paroxetine or desipramine seems to be equivalent. Finally, it is of interest that drugs that block the uptake of NE or 5-HT selectively produce therapeutic effects equivalent to drugs that block the uptake of both monoamines. At present, what we can state with confidence is that most depressives will respond to a drug that blocks the uptake of either NE or 5-HT or to one that blocks the uptake of both of these monoamines.

However, although we now have drugs that selectively block the reuptake of either NE or 5-HT, we also have antidepressants that essentially produce no inhibition of these reuptake processes or MAO. Table 1 indicates the potency (IC_{50} values) of various types of antidepressant drugs to inhibit the reuptake of NE or 5-HT. Secondary amine TCAs such as desipramine, nortriptyline, and protriptyline, as well as amoxapine and maprotiline among the second generation compounds, are relatively selective inhibitors of the reuptake of NE. As their class name implies, SSRIs are selective inhibitors of the reuptake of 5-HT. Interestingly, the magnitude of selectivity for fluoxetine is not that large, about 15-fold; fluoxetine, though, is an SSRI in humans.[119] Tertiary amine TCAs such as amitriptyline and imipramine, although slightly more potent in vitro as inhibitors of NE reuptake than 5-HT reuptake, do not exhibit any selectivity in vivo.[120] Interestingly, among the "nonselective" reuptake inhibitors, venlafaxine is the only one that is more potent in vitro for serotonin reuptake than NE reuptake. This raises the possibility that there may be dose regimens under which venlafaxine will function essentially as an SSRI. Further research will be needed to establish this.

Even among the TCAs, trimipramine is devoid of activity as a NE or 5-HT reuptake inhibitor, and doxepin also is a relatively weak inhibitor of the uptake of NE and especially 5-HT. Among the second generation antidepressant drugs, bupropion is a very weak inhibitor of the uptake of NE and 5-HT as is the newly marketed drug mirtazapine. Both trazodone and nefazodone are very weak inhibitors of NE reuptake and quite weak at inhibiting 5-HT reuptake also. Clearly, even though either the property of NE or 5-HT reuptake inhibition (or inhibition of MAO) is a good predictor of clinical efficacy as an antidepressant, some other property(ies) must account for the clinical efficacy of drugs such as trimipramine, bupropion, mirtazapine, and, perhaps, doxepin, nefazodone, and trazodone as well.

Among all antidepressant drugs, bupropion is relatively unique in that it more potently blocks the reuptake of dopamine than that of either NE or 5-HT.[121] It is also more potent in vivo as an inhibitor of dopamine reuptake than that of NE.[121] Bupropion may have dopamine mimetic properties in humans, as it decreases plasma concentrations of prolactin after its acute administration. On the other hand, treatment of patients with bupropion caused no decrease in the concentration of the dopamine metabolite homovanillic acid (HVA) in cerebrospinal fluid.[122] If inhibition of DA reuptake were occurring, a decrease in HVA would be expected.

Even though bupropion is slightly more potent in vitro and in vivo at inhibiting the reuptake of DA than that of NE, it is more potent in vivo in inhibiting the firing rate of noradrenergic soma in the locus ceruleus than it is at inhibiting the firing rate of dopaminergic cells in the midbrain.[121] Interestingly, treatment of patients with bupropion decreases whole-body NE turnover.[123] Thus, bupropion also seems capable of affecting noradrenergic transmission by a mechanism still to be determined. It seems possible that a metabolite of bupropion, in particular hydroxybupropion, might reach sufficient concentrations in patients to affect the reuptake of NE.[121]

The preceding discussion raises two issues. First, since not all antidepressant drugs block the reuptake of NE and/or 5-HT, what data exist from which it may be inferred that this pharmacologic property is important for efficacy among the antidepressant drugs that possess it? The relationship to clinical efficacy necessitates studies of depressed patients. Given this, it is difficult to state with certainty that reuptake inhibition is the essential feature needed for efficacy. However, there are data showing that the presence of 5-HT is necessary for the maintenance of an acute antidepressant effect of SSRIs (or MAOIs). It was found initially in the 1970s that administration of the inhibitor of 5-HT synthesis, parachlorophenylalanine (PCPA), rapidly reversed the antidepressant effects of either imipramine or tranylcypromine.[124] More recently, Delgado and associates[125,126] have reexamined this phenomenon using a different strategy. They gave patients who had responded to and were being maintained on antidepressant drugs a diet that was low in tryptophan and high in amino acids that compete with tryptophan for transport into the brain. As tryptophan is the dietary precursor of

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

5-HT, the effect of this diet is presumably to lower the brain content of 5-HT in the patients. This type of diet lowers levels of 5-HT in the brains of animals.[127] Administration of this diet produced a relapse in about 70% of the patients studied who were treated with an SSRI or MAOI, whereas only 20% of the "recovered" depressed patients treated with desipramine, nortriptyline, or bupropion relapsed.[126] Selective inhibitors of NE uptake, then, seem much less dependent on the availability of serotonin for their beneficial effects than do either SSRIs or MAOIs.

By contrast, selective inhibitors of NE uptake do seem dependent on the availability of NE for their effects, whereas the efficacy of SSRIs may not be. Administration of the inhibitor of catecholamine synthesis, alpha-methyl-para-tyrosine (AMPT), to recovered depressives maintained on antidepressants caused a return of depressive symptomatology in patients who responded to noradrenergic uptake inhibitors but not in those who responded to SSRIs.[128] It does seem, then, that antidepressants that inhibit NE and/or 5-HT reuptake, or inhibit MAO, need the availability of these transmitters for efficacy. Given this, for such drugs it seems reasonable to speculate that reuptake inhibition (or MAO inhibition) is a (the?) key pharmacologic property that contributes to antidepressant efficacy.

The second issue is what pharmacologic properties might contribute to efficacy among antidepressant drugs that have very little potency as inhibitors of either MAO or NE or 5-HT reuptake in vitro. Although 5-HT uptake in vivo has been speculated to be involved in the efficacy of nefazodone or trazodone,[129] this seems unlikely. For example, administration of nefazodone to rats produces either no inhibition of the serotonin transporter[130] or only modest inhibition even at high doses.[129] This is true of trazodone also.[131] Perhaps most importantly, administration of "therapeutic" doses of nefazodone (200 mg, b.i.d.) to healthy volunteers caused only a short-lived and modest inhibition (34%) of 5-HT uptake into platelets and no decrease of whole blood 5-HT content; this contrasts with the 50% to 80% decrease in whole blood 5-HT content produced by administration of 20 mg of fluoxetine.[132] In view of this, it seems highly unlikely that either drug causes much, if any, inhibition of 5-HT reuptake in patients treated with them. And if they do not inhibit 5-HT reuptake, they certainly do not inhibit NE reuptake (see Table 1).

A pharmacologic property shared by trazodone and nefazodone, as well as several TCAs and the new drug mirtazapine, is relatively high potency as an antagonist of a serotonin receptor called the 5-HT_{2A} receptor (Table 2). In general, these drugs are at least fivefold more potent in vitro as antagonists of this receptor than they are as inhibitors of 5-HT uptake (compare values in Table 2 with those in Table 1). It is not surprising, then, in studies of animals in vivo, these drugs more potently antagonize 5-HT_{2A}-mediated responses than they do 5-HT reuptake.[129–131,133–135] Interestingly, repeated administration to rats of those antidepressant drugs that are potent 5-HT_{2A} antagonists cause a down-regulation of 5-HT_{2A} receptors in the brain.[136–139] That antagonists down-regulate this receptor is somewhat surprising because down-regulation is usually associated with prolonged stimulation of a receptor by agonists. The mechanisms whereby antagonists cause down-regulation are unknown. Physical antagonism coupled with down-regulation of 5-HT_{2A} receptors certainly implies that these drugs are causing strong functional blockade of transmission mediated by 5-HT_{2A} receptors in vivo.

Table 2. Antidepressants With Relatively High Affinity for the 5-HT_{2A} Receptor*

Drug	K_i (nM)
Amitriptyline	18
Doxepin	25
Mirtazapine	10
Nefazodone	25
Nortriptyline	40
Trazodone	25

*Data from references 7 and 11.

Yet it is likely to be the enhancement of central serotonergic transmission that either contributes to or accounts for the efficacy of some TCAs, SSRIs, perhaps MAOIs, and venlafaxine (see above and reference 53). If such data are considered together, it seems reasonable to conclude, then, that such enhancement of serotonergic transmission is not occurring through activation of 5-HT_{2A} receptors (or probably 5-HT_{2C} receptors, also).

Even if these drugs are not 5-HT or NE reuptake inhibitors or MAOIs, might they still be capable of enhancing serotonergic or noradrenergic transmission? As is the case with many types of antidepressant drugs, chronic treatment of rats with trazodone causes desensitization of somatodendritic serotonin autoreceptors.[56] As activation of these autoreceptors exerts an inhibitory effect on serotonergic cell firing, their becoming desensitized might facilitate serotonergic transmission. Whether the structurally related nefazodone produces a similar effect is not yet known. However, chronic treatment of rats with nefazodone potentiates a response mediated by postsynaptic 5-HT_{1A} receptors.[138] Interestingly, acute treatment of rats with mirtazapine elicited a response mediated by 5-HT_{1A} receptors, even though this drug has very low potency for this receptor subtype.[135] There are a number of studies showing that altering the function of 5-HT_{2A} receptors modifies responses mediated by 5-HT_{1A} receptors and vice versa. How this occurs is currently the subject of considerable research, but is still unknown. Given this, however, it may be that the 5-HT_{2A} receptor antagonist properties of drugs such as trazodone, nefazodone, and mirtazapine contribute to facilitation of transmission mediated by postsynaptic 5-HT_{1A} receptors.

However, another factor to consider is that among all antidepressants, nefazodone and trazodone have the high-

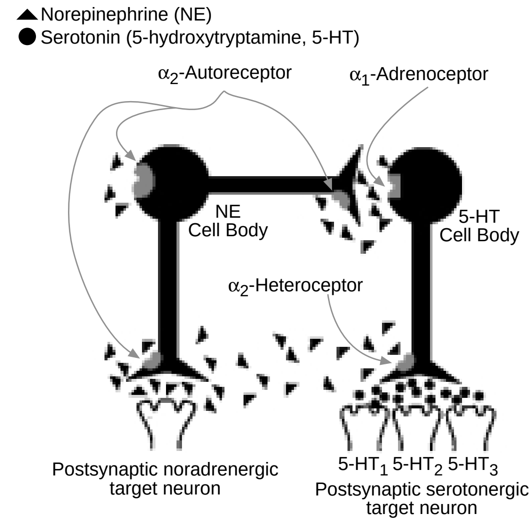
© Copyright Physicians Postgraduate Press, Inc.
One personal copy may be printed

est affinity (K_i values of about 100 nM) for the $5\text{-}HT_{1A}$ receptor.[11] As the therapeutic plasma concentrations of these two drugs are higher than those of other antidepressant drugs,[74,76] it seems probable that these two drugs do indeed cause some occupancy of $5\text{-}HT_{1A}$ receptors in vivo. Neither drug has been reported to cause $5\text{-}HT_{1A}$-mediated effects after their acute administration; it is therefore unlikely that they are $5\text{-}HT_{1A}$ agonists. It is more likely, therefore, that they are $5\text{-}HT_{1A}$ antagonists. However, the functional significance of $5\text{-}HT_{1A}$ antagonism is unclear.

Trazodone, trimipramine, and mirtazapine can facilitate noradrenergic transmission. Intravenous administration of trazodone to rats caused a modest, dose-dependent increase in the spontaneous firing rate of noradrenergic locus ceruleus neurons.[140] Interestingly, acute administration of trimipramine to rats caused the same effect.[141] Chronic treatment of rats with trimipramine caused a supersensitive response of cortical neurons to iontophoretically applied NE.[141] Such data indicate that both trazodone and trimipramine may facilitate noradrenergic transmission, even though the underlying mechanism(s) by which they do so is unknown.

Among existing antidepressant drugs, mirtazapine blocks α_2-adrenoceptors most potently (K_i = 100 nM).[7,11] Such α_2-adrenoceptor antagonism is produced in vivo by mirtazapine.[135] Both somatodendritic and terminal autoreceptors are the α_2 subtype. Consequently, antagonism of this receptor would enhance noradrenergic cell firing and the release of NE. The antagonism of α_2-adrenoceptors probably accounts for the ability of the acute administration of mirtazapine to increase the extracellular concentration of 3,4-dihydroxyphenylacetic acid (DOPAC) in the hippocampus, as measured using in vivo microdialysis.[135,142] In this study, the concentration of DOPAC was used to provide a measure of the release of NE. Thus, acute administration of mirtazapine enhances the release of NE. Not only can mirtazapine enhance noradrenergic transmission, but it can also facilitate serotonergic transmission as evidenced by its dose-dependent increase in the firing rate of serotonergic soma in the dorsal raphe nucleus.[143] Chemical lesioning of noradrenergic neurons prevented this effect of mirtazapine, indicating that the increase in serotonin cell firing was due to enhanced noradrenergic transmission. The enhancement of serotonergic cell firing is thought to be due to NE acting on α_1-adrenoceptors on the serotonergic soma and/or dendrites.[144] Thus, by blocking α_2-adrenoceptors, mirtazapine enhances the release of NE in the raphe nuclei which then activates α_1-adrenoceptors to increase the firing rate of serotonergic soma. This scenario is plausible as mirtazapine is about fourfold less potent in blocking α_1-adrenoceptors (K_i of about 400 nM)[7] than it is in blocking α_2-adrenoceptors. This is an important difference between mirtazapine and the structurally related drug mianserin. Mianserin has comparable potency at α_1- and α_2-adrenoceptors[7] and, consequently, does not produce a noradrenergic-induced enhancement of serotonergic transmission.[142]

Figure 8. Noradrenergic Regulation of the Release of 5-HT*



*Modified from reference 135, with permission. Noradrenergic nerves innervate the raphe nuclei. The enhanced release of norepinephrine in the raphe nuclei caused, for example, by blockade of inhibitory autoreceptors on noradrenergic terminals, activates postsynaptic α_1-adrenoceptors, which may lead to an increase of the rate of firing of serotonergic soma. This can lead to enhanced release of 5-HT at serotonergic terminals. In addition, there appear to be α_2-adrenoceptors on serotonergic terminals, which, when activated, can inhibit the release of 5-HT. Blockade, then, of such heteroceptors could further enhance the release of 5-HT.

The mirtazapine-induced increase in serotonergic cell firing causes enhanced release of 5-HT, measured using the technique of in vivo microdialysis.[135,142] The α_2-adrenoceptor-blocking activity of mirtazapine contributes in another way to this drug's facilitation of the release of 5-HT. The release of 5-HT from serotonergic terminals may be tonically inhibited by NE acting on α_2-adrenergic heteroceptors.[145] Mirtazapine antagonizes the inhibitory effect of NE on these heteroceptors,[143] thereby facilitating further the release of 5-HT.

The possible mechanisms by which NE can regulate the release of serotonin is shown schematically in Figure 8. It is evident from this figure that selective inhibitors of NE reuptake (e.g., desipramine, maprotiline) that are also potent α_1-adrenoceptor antagonists should not cause much enhancement of serotonergic transmission. Essentially all the selective NE reuptake inhibitors fall into this category (see Figure 6). These drugs are also very weak α_2-adrenoceptor antagonists,[11,117] so they would not facilitate 5-HT release by blocking α_2-adrenergic heteroceptors. Thus, although selective NE reuptake inhibitors may potentiate postsynaptically-mediated serotonergic electrophysiologic responses,[146] other pharmacologic properties that they either possess (α_1 antagonism) or lack (α_2 antagonism) make them unlikely to facilitate serotonergic transmission through noradrenergic mechanisms.

© Copyright 1997 Physicians Postgraduate Press, Inc. One personal copy may be printed

The converse issue to that just discussed is whether altered serotonergic transmission leads to changes in noradrenergic transmission. Serotonergic innervation of the locus ceruleus[147] provides the anatomic basis for such a possibility. Iontophoretic application of 5-HT into the locus ceruleus can cause suppression of its spontaneous firing rate, but this effect is inconsistent.[148,149] However, there does appear to be a serotonergic inhibitory pathway between the dorsal raphe nucleus and the locus ceruleus that markedly attenuates the excitation of the locus ceruleus caused by a noxious stimulus.[148,150] The excitatory response of the locus ceruleus to noxious stimuli appears to be mediated by an excitatory amino acid pathway.[151] The observation, then, that iontophoretic administration of 5-HT into the locus ceruleus reliably attenuated the excitation of the locus ceruleus caused by glutamate or kainate[149] implies that 5-HT may block locus ceruleus responses to painful stimuli by attenuating responses of locus ceruleus neurons to excitatory amino acids. A 5-HT_{1A} receptor may mediate this effect of 5-HT.[152] The precise site of action in the locus ceruleus whereby 5-HT produces these effects on excitatory amino acid responses is unclear. In addition, there appears to be a site outside the locus ceruleus where activation of 5-HT_{2A} receptors increases locus ceruleus responses to somatosensory stimulation.[153]

Thus, although serotonergic transmission may not directly modulate the activity of locus ceruleus neurons, it may modulate the response of locus ceruleus neurons to other inputs, particularly those using excitatory amino acid transmitters such as glutamate. In general, though, it appears that the locus ceruleus is not under the type of direct influence from its serotonergic innervation that the dorsal raphe is by its noradrenergic innervation. What effect, if any, then, that antidepressants selectively acting on serotonergic neurons (e.g., SSRIs) would have indirectly on noradrenergic transmission remains a matter of conjecture.

CONCLUSION

Several points emerge from the foregoing discussion. First, most available antidepressant drugs that are selective for noradrenergic neurons are unlikely to have a secondary effect on serotonergic neuronal activity and the release of 5-HT. Second, serotonin selective antidepressant drugs seem even more unlikely to modulate noradrenergic neuronal firing and release. This might explain why on a variety of serotonergic and noradrenergic parameters, long-term effects caused by antidepressant drugs seem dependent on their acute pharmacologic properties, i.e., noradrenergic but not serotonergic drugs modify noradrenergic parameters, and serotonergic but not noradrenergic drugs alter serotonergic indices. Ordway et al.[54] reported that the decrease in density of β-adrenoceptors throughout the brain caused by antidepressant drugs was confined to those drugs that had acute noradrenergic effects; neither SSRIs nor trazodone produced this effect. The ability of antidepressant drugs to reduce responses elicited by activation of 5-HT_{1A} receptors upon repeated administration seems limited to those drugs that block the uptake of serotonin or inhibit its catabolism.[154] Similarly, antidepressant-induced desensitization of α_2-adrenoceptors on 5-HT terminals was caused by a reversible MAOI and a selective inhibitor of NE uptake, but not by an SSRI.[155] Such selectivity of action is also consistent with the clinical data mentioned earlier,[126,128] whereby selective inhibitors of NE reuptake seem dependent on the availability of NE but not 5-HT for their efficacy, whereas SSRIs need 5-HT but not NE for their beneficial effects.

Third, there are novel and, in some instances, still unexplained mechanisms by which antidepressants that are neither reuptake inhibitors nor MAOIs facilitate serotonergic- and/or noradrenergic-mediated responses. A key area for future research will be to understand these mechanisms.

Drug names: amitriptyline (Elavil and others), amoxapine (Asendin), amphetamine (Adderall), bupropion (Wellbutrin), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), midazolam (Versed), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor), paroxetine (Paxil), phenelzine (Nardil), protriptyline (Vivactil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel), trimipramine (Surmontil), venlafaxine (Effexor).

REFERENCES

1. Keith SJ, Matthews SM. The value of psychiatric treatment: its efficacy in severe mental disorders. Psychopharmacol Bull 1993;29:427–430
2. Richelson E. The pharmacology of antidepressants at the synapse: focus on newer compounds. J Clin Psychiatry 1994;55(9, suppl A):34–39
3. Sigg EB. Tricyclic thymoleptic agents and some newer antidepressants. In: Efron DH, ed. Psychopharmacology: A Review of Progress. Washington, DC: US Government Printing Office; 1968:655–669
4. Amrein R, Allen SR, Guentert TW, et al. The pharmacology of reversible monoamine oxidase inhibitors. Br J Psychiatry 1989;155(6, suppl):66–71
5. Haefely W, Burkard WP, Cesura AM, et al. Biochemistry and pharmacology of moclobemide, a prototype RIMA. Psychopharmacology 1992;106: S6–S14
6. Burton SW. A review of fluvoxamine and its uses in depression. Int Clin Psychopharmacol 1991;6(3, suppl):1–21
7. De Boer TH, Maura G, Raiteri M, et al. Neurochemical and autonomic pharmacological profiles of the 6-AZA-analogue of mianserin, ORG 3770 and its enantiomers. Neuropharmacology 1988;27:399–408
8. Richelson E. Biological basis of depression and therapeutic relevance. J Clin Psychiatry 1991;52(6, suppl):4–10
9. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci 1993;52:1023–1029
10. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984;230: 94–102
11. Cusack B, Nelson A, Eichelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology 1994;114:559–565
12. Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 1958;115:459–464
13. Olfson M, Klerman GL. Trends in the prescription of antidepressants by office-based psychiatrists. Am J Psychiatry 1993;150:571–577
14. Klerman GL, Cole JO. Clinical pharmacology of imipramine and related

© Copyright 1997 Physicians Postgraduate Press, Inc. One personal copy may be printed

antidepressant compounds. Pharmacol Rev 1965;17:101–141
15. Klein DF, Gittelman R, Quitkin F, et al. Diagnosis and Drug Treatment of Psychiatric Disorders. 2nd ed. Baltimore, Md: Williams and Wilkins; 1980
16. Brotman AW, Falk WE. Pharmacologic treatment of acute depressive subtypes. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987:1031–1040
17. Quitkin FM, McGrath PJ, Stewart JW, et al. Atypical depression, panic attacks, and response to imipramine and phenelzine. Arch Gen Psychiatry 1990;47:935–941
18. Kocsis JH, Croughan JL, Katz MM, et al. Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. Am J Psychiatry 1990;147: 621–624
19. Kline NS. Clinical experience with iproniazid (MARSILID). J Clin Exp Psychopathol 1958;19(suppl 1):72–78
20. Crane GE. Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating disease. Psychiatric Research Reports of the American Psychiatric Association 1959;8:142–152
21. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185–219
22. Quitkin F, Rifkin A, Klein DF. Monoamine oxidase inhibitors: a review of antidepressant effectiveness. Arch Gen Psychiatry 1979;36:749–760
23. Murphy DL, Aulakh CS, Garrick NA. Monoamine oxidase inhibitors as antidepressants: implications for the mechanism of action of antidepressants and the psychobiology of the affective disorders and some related disorders. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987:545–552
24. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988;45:129–139
25. Quitkin FM, Harrison W, Stewart JW, et al. Response to phenelzine and imipramine in placebo nonresponders with atypical depression: a new application of the crossover design. Arch Gen Psychiatry 1991;48:319–323
26. Nolen WA, Haffmans J. Treatment resistant depression: review on the efficacy of various biological treatments, specifically in major depression resistant to cyclic antidepressants. Int Clin Psychopharmacol 1989;4: 217–228
27. Thase ME, Frank E, Mallinger AG, et al. Treatment of imipramine-resistant recurrent depression, III: efficacy of monoamine oxidase inhibitors. J Clin Psychiatry 1992;53:5–11
28. McGrath PJ, Stewart JW, Nunes EV, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. Am J Psychiatry 1993;150:118–123
29. Shih JC. Molecular basis of human MAO A and B. Neuropsychopharmacology 1991;4:1–7
30. Mann JJ, Aarons SF, Wilner PJ, et al. A controlled study of the antidepressant efficacy and side effects of (-)-deprenyl. Arch Gen Psychiatry 1989;46:435–450
31. Workman EA, Short DD. Atypical antidepressants versus imipramine in the treatment of major depression: a meta-analysis. J Clin Psychiatry 1993;54:5–12
32. Kinney JL, Evans RL Jr. Evaluation of amoxapine. Clinical Pharmacy 1982;1:417–424
33. Gruter W, Poldinger W. Maprotiline. Mod Probl Pharmacopsychiatry 1982; 18:17–48
34. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. J Clin Psychiatry 1983;44(5, Sec 2):148–152
35. Rickels K, Schweizer E. Clinical overview of serotonin reuptake inhibitors. J Clin Psychiatry 1990;51(12, suppl B):9–12
36. Kasper S, Fuger J, Moller H-J. Comparative efficacy of antidepressants. Drugs 1992;43(2, suppl):11–23
37. Dechant KL, Clissold P. Paroxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 1991;41:225–253
38. Grimsley SR, Jann MW. Paroxetine, sertraline, and fluoxetine: new selective serotonin reuptake inhibitors. Clinical Pharmacy 1992;11:930–957
39. Murdoch D, McTavish D. Sertraline: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 1992;44:604–624
40. Montgomery SA. Selective serotonin reuptake inhibitors in the acute treatment of depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995: 1043–1051
41. Guelfi JD, White C, Hackett D. Effectiveness of venlafaxine in patients hospitalized with major depression and melancholia. J Clin Psychiatry 1995;56:450–458
42. Schweizer E, Feighner J, Mandos L, et al. Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. J Clin Psychiatry 1994;55:104–108
43. Cunningham LA, Borison RL, Carman JS, et al. A comparison of venlafaxine, trazodone, and placebo in major depression. J Clin Psychopharmacol 1994;14:99–106
44. Rickels K, Robinson DS, Schweizer E, et al. Nefazodone: aspects of efficacy. J Clin Psychiatry 1995;56(6, suppl):43–46
45. Sitsen JMA, Zivkov M. Mirtazapine: clinical profile. CNS Drugs 1995;(4, suppl):39–48
46. Claghorn JL, Lesem MD. A double-blind placebo-controlled study of Org 3770 in depressed outpatients. J Affect Disord 1995;34:165–171
47. Zivkov M, De Jongh GD. Org 3770 versus amitriptyline: a 6-week randomized double-blind multicentre trial in hospitalized depressed patients. Human Psychopharmacology 1995;10:173–180
48. van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol 1995;10:3–9
49. Frazer A, Conway P. Pharmacologic mechanisms of action of antidepressants. Psychiatr Clin North Am 1984;7:575–586
50. de Montigny C, Chaput Y, Blier P. Modification of serotonergic neuron properties by long-term treatment with serotonin reuptake blockers. J Clin Psychiatry 1990;51(12, suppl B):4–8
51. Frazer A, Pandey G, Mendels J, et al. The effect of triiodothyronine on [^{3}H]-cyclic AMP production in slices of rat cerebral cortex. Neuropharmacology 1974;13:1131–1140
52. Vetulani J, Sulser F. Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. Nature 1975;257:495–496
53. Banerjee SP, Kung LS, Chanda SK. Development of β adrenergic receptor subsensitivity by antidepressants. Nature 1977;268:455–456
54. Ordway GA, Gambarana C, Tejani-Butt SM, et al. Preferential reduction of binding of ^{125} l-iodopindolol to beta-1 adrenoceptors in the amygdala of rat after antidepressant treatments. J Pharmacol Exp Ther 1991;257:681–690
55. Aghajanian GK. Feedback regulation of central monoaminergic neurons: evidence from single cell recording studies. In: Youdim MBH, Lovenberg W, Sharman DF, et al, eds. Essays in Neurochemistry and Neuropharmacology, vol 3. New York, NY: John Wiley & Sons; 1978:1–33
56. Blier P, de Montigny C, Chaput Y. Modifications of the serotonin system by antidepressant treatments: implications for the therapeutic response in major depression. J Clin Psychopharmacol 1987;7:24S–35S
57. Sulser F. Functional aspects of the norepinephrine receptor coupled adenylate cyclase system in the limbic forebrain and its modification by drugs which precipitate or alleviate depression: molecular approaches to an understanding of affective disorders. Pharmakopsychiatr Neuro Psychopharm 1978;11:43–52
58. Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994;15:220–226
59. George MS, Lydiard RB. Speed of onset of action of the newer antidepressants—fluoxetine and bupropion. Int Clin Psychopharmacol 1991;6: 209–217
60. Burke MJ, Preskorn SH. Short-term treatment of mood disorders with standard antidepressants. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1053–1065
61. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
62. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
63. Khan A, Cohen S, Dager S, et al. Onset of response in relation to outcome in depressed outpatients with placebo and imipramine. J Affect Disord 1989;17:33–38
64. Prien RF, Blaine JD, Levine J. Antidepressant drug therapy: the role of the new antidepressants. Hosp Community Psychiatry 1985;36:513–516
65. Rickels K, Derivan A, Entsuah R, et al. Rapid onset of antidepressant activity with venlafaxine treatment. Depression 1995;3:146–153
66. Tollefson GD, Holman SL. How long to onset of antidepressant action: a meta-analysis of patients treated with fluoxetine or placebo. Int Clin Psychopharmacol 1994;9:245–250
67. Lader M, Lang RA, Wilson GD. Patterns of improvement of depressed inpatients. In: Maudsley Monograph No. 30. New York, NY: Oxford Univer-

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

sity Press; 1987
68. Small JG, Milstein V, Kellams JJ, et al. Comparative onset on improvement in depressive symptomatology with drug treatment, electroconvulsive therapy, and placebo. J Clin Psychopharmacol 1981;1:62S–69S
69 Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. Eur Neuropsychopharmacol 1993;3:127–135
70. Katz MM, Koscow SH, Maas JW, et al. The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychol Med 1987;17:297–309
71. Tollefson GD. Antidepressant treatment and side effect considerations. J Clin Psychiatry 1991;52:(5, suppl)4–13
72. Boyer WF, Blumhardt CL. The safety profile of paroxetine. J Clin Psychiatry 1992;53(2, suppl):61–66
73. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10(4, suppl):37–45
74. Preskorn SH. Pharmacokinetics of antidepressants: why and how they are relevant to treatment. J Clin Psychiatry 1993;54(9, suppl):14–34
75. Salazar DE, Dockens RC, Milbrath RL, et al. Pharmacokinetic and pharmacodynamic evaluation of warfarin and nefazodone coadministration in healthy subjects. J Clin Pharmacol 1995;35:730–738
76. Barbhaiya RH, Buch AB, Greene DS. A study of the effect of age and gender on the pharmacokinetics of nefazodone after single and multiple doses. J Clin Psychopharmacology 1996;16:19–25
77. Aston-Jones G, Chiang C, Alexinsky T. Discharge of noradrenergic locus ceruleus neurons in behaving rats and monkeys suggests a role in vigilance. Prog Brain Res 1991;88:501–520
78. Warrington SJ, Padgham C, Lader M. The cardiovascular effects of antidepressants. Psychol Med Monogr Suppl 1989;19(suppl 16):1–40
79. Bryant SG, Ereshefsky L. Antidepressant properties of trazodone. Clinical Pharmacy 1982;1:406–417
80. Rudolph RL, Derivan A. The safety and tolerability of venlafaxine hydrochloride: analysis of the clinical trials database. J Clin Psychopharmacol 1996;16(suppl 2):54S–59S
81. Roose SP, Glassman AH, Giardina EG, et al. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. J Clin Psychopharmacol 1987;7:247–251
82. Cole JO, Brodkin JA. Antidepressant drug side effects. J Clin Psychiatry 1990;51(1, suppl):21–26
83. Fernstrom MH, Kupfer DJ. Antidepressant-induced weight gain: a comparison study of four medications. Psychiatry Res 1988;26:265–271
84. Harto-Traux N, Stern WC, Miller LL, et al. Effects of bupropion on body weight. J Clin Psychiatry 1983;44(5, sec 2):183–186
85. Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. Drug Safety 1994;10:18–46
86. Skowron DM, Stimmel GL. Antidepressants and the risk of seizures. Pharmacotherapy 1992;12:18–22
87. Krijzer F, Snelder M, Bradford D. Comparison of the (pro)convulsive properties of fluvoxamine and clovoxamine with eight other antidepressants in an animal model. Neuropsychobiology 1984;12:249–254
88. Wagner W, Plekkenpol B, Gray TE, et al. Review of fluvoxamine safety database. Drugs 1992;43(2, suppl):48–54
89. Preskorn SH, Fast GA. Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. J Clin Psychiatry 1991;52(6, suppl): 23–33
90. Fogelson DL, Bystritsky A, Pasnau R. Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 1992;53:443–446
91. Sachs GA, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393
92. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 1995;56(6, suppl):12–21
93. Davidson JRT. Sexual dysfunction and antidepressants. Depression 1994/1995;2:233–240
94. Segraves RT. Overview of sexual dysfunction complicating the treatment of depression. J Clin Psychiatry Monograph 1992;10:4–10
95. Gardner EA, Johnston JA. Bupropion—an antidepressant without sexual pathophysiological action. J Clin Psychopharmacol 1985;5:24–29
96. Sher M, Krieger NJ, Juergens S. Trazodone and priapism. Am J Psychiatry 1983;140:1362–1363
97. Warner MD, Peabody CA, Whiteford HA, et al. Trazodone and priapism. J Clin Psychiatry 1987;48:244–245
98. Jue SG, Dawson GW, Brogden RN. Amoxapine: a review of its pharmacology and efficacy in depressed states. Drugs 1982;24:1–23
99. Kapur S, Mieczkowski T, Mann JJ. Antidepressant medications and the relative risk of suicide attempt and suicide. JAMA 1992;268:3441–3445
100. Montgomery SA. Suicide and antidepressants. Drugs 1992;43:24–31
101. Crome P, Newman B. Fatal tricyclic antidepressant poisoning. J R Soc Med 1979;72:649–653
102. Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. BMJ 1987;295:1021–1024
103. de Jonghe F, Swinkels JA. The safety of antidepressants. Drugs 1992;43 (2, suppl):40–46
104. Blackwell B. Hypertensive crisis due to monoamine oxidase inhibitors. Lancet 1963;ii:849–851
105. Cooper AJ. Tyramine and irreversible monoamine oxidase inhibitors in clinical practice. Br J Psychiatry 1989;155(6, suppl):38–45
106. Da Prada M, Zurcher G, Wuthrich I, et al. On tyramine, food, beverages and the reversible MAO inhibitor moclobemide. J Neural Transm Suppl 1988;26:S31–S56
107. Sullivan EA, Shulman KI. Diet and monoamine oxidase inhibitors: a reexamination. Can J Psychiatry 1984;29:707–711
108. Hill S, Yau K, Whitwam J. MAOIs to RIMAs in anesthesia: a literature review. Psychopharmacology 1992;106:S43–S45
109. Meredith TJ, Vale JA. Poisoning due to psychotropic agents. Adverse Drug Reactions and Acute Poisoning Reviews 1985;4:83–126
110. Linden CH, Rumack BH, Strehlke C. Monoamine oxidase inhibitor overdose. Ann Emerg Med 1984;13:1137–1144
111. Van Wyck Fleet J, Manberg PJ, Miller LL, et al. Overview of clinically significant adverse reactions to bupropion. J Clin Psychiatry 1983;44(5, sec 2):191–196
112. Spiller HA, Ramoska EA, Krenzelok EP, et al. Bupropion overdose: a 3-year multi-center retrospective analysis. Am J Emerg Med 1994;12: 43–45
113. Prange AJ Jr. The pharmacology and biochemistry of depression. Dis Nerv Syst 1964;25:217–221
114. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122:509–522
115. Coppen A. The biochemistry of affective disorders. Br J Psychiatry 1967;113:1237–1264
116. Lapin IP, Oxenkrug GF. Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect. Lancet 1969;1:132–136
117. Janowsky DS, El-Yousef MK, Davis JM, et al. A cholinergic-adrenergic hypothesis of mania and depression. Lancet 1972;2:632–635
118. Carlsson A, Corrodi H, Fuxe K, et al. Effect of antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethyl-meta-tyramine. Eur J Pharmacol 1969;5:357–366
119. Lemberger L, Rowe H, Carmichael R, et al. Fluoxetine, a selective serotonin uptake inhibitor. Clin Pharmacol Ther 1978;23:421–429
120. Bowden CL, Koslow SH, Hanin I, et al. Effects of amitriptyline and imipramine on brain amine neurotransmitter metabolites in cerebrospinal fluid. Clin Pharmacol Ther 1985;37:316–324
121. Ascher JA, Cole JO, Colin J-N, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401
122. Golden RN, Rudorfer MV, Sherer MA, et al. Bupropion in depression, I: biochemical effects and clinical response. Arch Gen Psychiatry 1988; 45:139–143
123. Golden RN, DeVane CL, Laizure SC, et al. Bupropion in depression, II: the role of metabolites in clinical outcome. Arch Gen Psychiatry 1988;45:145–149
124. Shopsin B, Friedman E, Gershon S. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patients. Arch Gen Psychiatry 1976;33:811–819
125. Delgado PL, Charney DS, Price LH, et al. Serotonin function and the mechanism of antidepressant action: reversal of antidepressant induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry 1990;47:411–418
126. Delgado PL, Price LH, Miller HL. Rapid serotonin depletion as a provocative challenge test for patients with major depression: relevance to antidepressant action and the neurobiology of depression. Psychopharmacol Bull 1991;27:321–330
127. Moja EA, Cipollo P, Castoldi D, et al. Dose-response decrease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino acid mixtures in rats. Life Sci 1989;44:971–976
128. Delgado PL, Miller HL, Salomon RM, et al. Monoamines and the mech-

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed

anism of antidepressant action: effects of catecholamine depletion on mood of patients treated with antidepressants. Psychopharmacol Bull 1993;29:389–396
129. Taylor DP, Carter RB, Eison AS, et al. Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. J Clin Psychiatry 1995;56 (6, suppl):3–11
130. Hemrick-Luecke SK, Snoddy HD, Fuller RW. Evaluation of nefazodone as a serotonin uptake inhibitor and a serotonin antagonist in vivo. Life Sci 1994;55:479–483
131. Fuller RW, Snoddy HD, Cohen ML. Interactions of trazodone with serotonin neurons and receptors. Neuropharmacology 1984;23:539–544
132. Salazar DE, Chaikin PC, Swanson BN, et al. The effects of nefazodone and fluoxetine on platelet serotonin-uptake and whole blood serotonin. Clin Pharmacol Ther 1994;55:137
133. Maj J, Palider W, Rawlow A. Trazodone: a central serotonin antagonist and agonist. J Neural Transm 1979;44:237–248
134. Clements-Jewery S, Robson PA, Chidley LJ. Biochemical investigations into the mode of action of trazodone. Neuropharmacology 1980;19: 1165–1173
135. De Boer TH, Ruigt GSF, Berendsen HHG. The α_2-selective adrenoceptor antagonist Org 3770 (Mirtazapine, Remeron) enhances noradrenergic and serotonergic transmission. Human Psychopharmacology 1995;10: S107–S118
136. Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. Science 1980;210:88–90
137. Enna SJ, Kendall DA. Interaction of antidepressants and brain neurotransmitter receptors. J Clin Psychopharmacol 1981;1:12S–16S
138. Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990;26:311–315
139. Berendsen RRG, Borekkamp CLE, van Delft AML. Down regulation of 5-HT_{2A} receptors after chronic treatment with remeron. Eur Neuropsychopharmacol 1995;5:306
140. VanderMaelen CP, Braselton JP. Acute administration of the antidepressant trazodone increases noradrenergic locus ceruleus neuronal firing in rats. Archives Internationales de Pharmacodyamie et de Therapie 1990;308:13–20
141. Hauser K, Olpe H-R, Jones RSG. Trimipramine, a tricyclic antidepressant exerting atypical actions on the central noradrenergic system. Eur J Pharmacol 1985;111:23–30
142. De Boer TH, Nefkens E, van Helvoirt A, et al. Differences in modulation of noradrenergic and serotonergic transmission by the α_2-adrenoceptor antagonists mirtazapine, mianserin and idazoxan. J Pharmacol Exp Ther 1996;277:852–860
143. Haddjeri N, Blier P, de Montigny C. Effect of the α_2-adrenoceptor antagonist mirtazapine on the 5-hydroxytryptamine system in the rat brain. J Pharmacol Exp Ther. In press
144. Baraban JM, Aghajanian GK. Suppression of firing activity of 5-HT neurons in the dorsal raphe by alpha-adrenoceptor antagonists. Neuropharmacology 1980;19:355–363
145. Mongeau R, Blier P, de Montigny C. In vivo electrophysiological evidence for tonic activation by endogenous noradrenaline on α_2 adrenergic heteroreceptors of 5-hydroxytryptamine terminals in the rat hippocampus. Naunyn-Schmiedebergs Archives of Pharmacology 1993; 347:266–272
146. de Montigny C, Aghajanian GK. Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. Science 1978;202:1303–1306
147. Pickel VM, Joh TH, Chan J, et al. Serotonergic terminals: ultrastructure and synaptic interaction with catecholamine-containing neurons in the medial nuclei of the solitary tracts. J Comp Neurol 1984;225:291–301
148. Segal M. Serotonergic innervation of the locus ceruleus from the dorsal raphe and its actions on responses to noxious stimuli. J Physiol (Lond) 1979;286:401–415
149. Aston-Jones G, Akaoka H, Charlety P, et al. Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus ceruleus neurons. J Neurosci 1991;11:760–769
150. Shiekhattar R, Aston-Jones G. Sensory responsiveness of brain noradrenergic neurons is modulated by endogenous brain serotonin. Brain Res 1993;623:72–76
151. Ennis M, Aston-Jones G. Activation of locus ceruleus from nucleus paragigantocellularis: a new excitatory amino acid pathway in brain. J Neurosci 1988;8:3644–3657
152. Aston-Jones G, Charlety P, Akaoka H, et al. Serotonin acts at 5-HT_{1A} receptors to selectively attenuate glutamate-evoked responses of locus ceruleus neurons. Society for Neuroscience 1990;16:799
153. Chiang C, Aston-Jones G. A $5\text{-hydroxytryptamine}_2$ agonist augments γ-aminobutyric acid and excitatory amino acid inputs to noradrenergic locus ceruleus neurons. Neuroscience 1993;54:409–420
154. Hensler JG, Kovachich GB, Frazer A. A quantitative autoradiographic study of serotonin_{1A} receptor regulation: effect of 5,7-dihydroxytryptamine and antidepressant treatments. Neuropsychopharmacology 1991; 4:131–144
155. Mongeau R, de Montigny C. Electrophysiologic evidence for desensitization of α_2-adrenoceptors on serotonin terminals following long-term treatment with drugs increasing norepinephrine synaptic concentration. Neuropsychopharmacology 1994;10:41–51

© Copyright 1997 Physicians Postgraduate Press, Inc.
One personal copy may be printed