Differential Pharmacology of Newer Antidepressants

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New antidepressants have become available for clinical use in the 1990s. Before this decade, the drugs available to treat depression consisted essentially of lithium, the monoamine oxidase inhibitors, and tricyclic antidepressants. Trazodone and bupropion, introduced in the mid-1980s, were the first major departures from the pharmacology of the tricyclics. Following the introduction in 1988 of the first serotonin selective reuptake inhibitor (SSRI) in the United States, the options have expanded and now include four SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine), nefazodone, venlafaxine, and mirtazapine. Citalopram and reboxetine are expected to be available by the end of the decade. These newer drugs possess a variety of pharmacological characteristics that are relevant to the choice of an antidepressant for clinical use. This review summarizes some of the major pharmacokinetic and pharmacodynamic similarities and differences among these drugs.

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The number of available antidepressants has expanded appreciably during the 1990s. There will soon be ten compounds available for clinical use in addition to the tricyclics (TCA), monoamine oxidase inhibitors, trazodone, amoxapine, and maprotiline. These older drugs have provided the benchmarks of efficacy and tolerability by which subsequent antidepressants have been evaluated, but they no longer capture the research or clinical interest of their putative replacements. The TCAs have generally been considered a homogeneous group of drugs, differing mostly in their potency to inhibit presynaptic norepinephrine or serotonin uptake and in their propensity for causing certain side effects.[1] The improved safety, tolerability, and broad therapeutic actions of the newer drugs have resulted in displacement of the TCAs as the first-choice drugs for treating recurrent major depression.[2]

The serotonin selective reuptake inhibitors (SSRIs) are now the most widely utilized class of antidepressants in clinical practice. The introduction of fluoxetine in 1988 was soon followed by sertraline, paroxetine, and fluvoxamine, respectively. Fluvoxamine is labeled only for the treatment of obsessive-compulsive disorder in the United States but is extensively used as an antidepressant in other countries. Subsequently available antidepressants include venlafaxine, nefazodone, and mirtazapine. Citalopram is an SSRI widely used in Europe and is expected to be marketed soon in the U.S. Reboxetine, a presynaptic uptake inhibitor of norepinephrine, should also soon become available.[3,4] Since 1988, the clinician who must select an agent for the treatment of depression has gained a wide array of choices and opportunities. The purpose of this review is to summarize some of the major pharmacologic characteristics of the newer antidepressants. Bupropion is included in this category due to its unique pharmacologic properties. My intent is not to be exhaustive but to highlight some of the differences and similarities that may aid the clinician in the choice of an antidepressant for a particular patient.

The pharmacologic differentiation of antidepressants is divided in Table 1 into 3 broad categories. These are physicochemical, pharmacodynamic, and pharmacokinetic properties. This list is not exclusive to the antidepressants but can apply broadly to all categories of psychoactive drugs. Specific properties may assume greater significance for a particular class of drugs. For example, an effect on respiration is not normally a consideration in choosing an antidepressant but may become relevant in the selection of a sedative-hypnotic or anxiolytic agent, particularly for a patient with chronic pulmonary disease. Among patients who receive clozapine, respiratory distress was experienced by a few patients who were also administered benzodiazepines.[5] However, a similar association has not been reported with other atypical antipsychotics. In patients with comorbid alcohol or other substance dependence disorders, consideration of a drug's propensity to support cross-tolerance and physical dependence often assumes primary importance.

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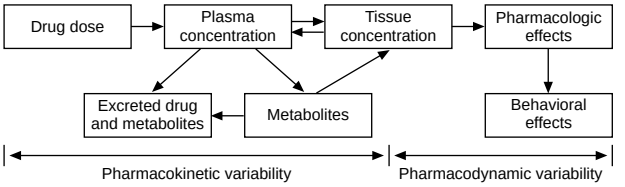
Table 1. Areas of Pharmacologic Differentiation of Antidepressants

Physicochemical Properties
Structure
Lipid solubility
Stereochemistry
Pharmacodynamic Properties
Receptor pharmacology (presynaptic and postsynaptic effects)
Neurotransmitter effects
Sleep architecture
Cardiovascular effects
Respiratory effects
Psychomotor function, cognition, and complex behavior
Endocrine and sexual functioning
Therapeutic uses (efficacy/effectiveness in depression, anxiety, and other disorders)
Side effects, tolerability, and toxicity
Pharmacokinetic Properties
Absorption
Distribution
Metabolism
Elimination
Effects of altered physiological states (renal, hepatic impairment, obesity, pregnancy)
Effects of aging, gender, menstrual cycle
Interactions with drug-metabolizing enzymes and other drugs

The properties in Table 1 serve only as guidelines for comparing some of the fundamental pharmacologic characteristics of antidepressants. Further data relating to efficacy and safety are prerequisite considerations when choosing specific agents for individuals, as well as history of response. For example, in a depressed patient with comorbid panic disorder, the choice of an SSRI would be logical due to these drugs' demonstrated antipanic properties.[6] In contrast, bupropion lacks substantial evidence of efficacy in the treatment of anxiety disorders.

An antidepressant's pharmacokinetic and pharmacodynamic properties are especially important, as variability in these properties are major determinants of the dose-effect relationship in patients, which is shown in Figure 1. More is known about pharmacokinetic variability among the antidepressants and its causes, as this source of variability is much easier to measure than pharmacodynamic variability.[7] For example, the genetic polymorphism of several hepatic enzymes results in much higher than expected plasma concentrations of some antidepressants in 6% to 10% of Caucasian populations in Europe and North America.[8,9] A comparable insight is lacking into genetically-based differences in neuroreceptor subtypes between patients, which we presume to be involved in mediating the therapeutic response from administered antidepressants. Some preliminary data[10,11] support the existence of different phenotypes of serotonin and dopamine receptors, which may be important determinants of the response to atypical antipsychotics. As genetic investigations using techniques from molecular biology will continue to be a research focus, more will be learned about the genetic contribution to the pharmacodynamic variability of antidepressant response.

Figure 1. Pharmacokinetic and Pharmacodynamic Variability as Determinants of the Dose-Effect Relationship*



*Adapted from reference 7.

PHYSICOCHEMICAL CHARACTERISTICS

Physical and chemical properties of antidepressants are major determinants of their pharmacokinetic properties and therefore of the dose-effect relationship (Figure 1). However, physicochemical properties are not usually considered important in the selection of an antidepressant. These characteristics are routinely assessed in preclinical studies when candidate molecules are accepted or rejected for clinical drug development programs. Nevertheless, the physicochemical differences among available antidepressants can be dramatic, and an appreciation of some differences can contribute to an understanding of the drugs' differential pharmacology.

Structure

Differences in chemical structure are apparent with the newer antidepressants, as they are representative of a variety of chemical drug classes. All the newer antidepressants are synthesized compounds, and none are derived from natural sources. A common characteristic they share is a molecular weight generally between 300 and 500, which categorizes them as relatively small molecules. This small size, along with a balance between water and lipid solubility, confers upon the antidepressants the ability to be absorbed easily across mucus membranes. Thus, bioavailability and access to the circulation upon oral administration is relatively high, although the different antidepressants undergo varying degrees of first-pass elimination in the gut wall and liver during the absorption process.[12] A high oral bioavailability is a desirable characteristic, as poor bioavailability by definition is variable bioavailability. Variability in oral absorption can contribute to differences in steady-state plasma drug concentration between patients. This situation undermines the predictability of a consistent dose-effect relationship (Figure 1).

In comparison to the currently available drugs, more antidepressants of the future are expected to be based on peptide structures derived from proteins. These large molecular weight compounds frequently lack stability against biodegradation and penetrate membrane barriers poorly, resulting in problems of oral bioavailability. This characteristic may necessitate special oral formulations or administration by the intravenous route.[13]

Table 2. Stereochemistry of Newer Antidepressants and Metabolites

Drug	Relevant Compounds in Plasma
Fluoxetine	(S)-fluoxetine; (R)-fluoxetine; (S)-norfluoxetine; (R)-norfluoxetine
Sertraline	(cis)-sertraline
Paroxetine	(trans)-paroxetine
Citalopram	(S)-citalopram; (R)-citalopram; (S)-desmethylcitalopram; (R)-desmethylcitalopram
Venlafaxine	(R)-venlafaxine; (S)-venlafaxine; (R)-O-desmethylvenlafaxine; (S)-O-desmethylvenlafaxine
Mirtazapine	(+)-mirtazapine; (–)-mirtazapine
Reboxetine	(R)-reboxetine; (S)-reboxetine

Lipid Solubility

An important consideration for drugs acting in the central nervous system (CNS) is their degree of lipid solubility (Table 1). Sufficient fat solubility is necessary for antidepressants both to be absorbed across mucous membranes of the gastrointestinal tract and also to pass through the blood brain barrier. In addition to promoting CNS penetration, lipid solubility also contributes to wide distribution of drugs in tissues throughout the body. For this reason, the tricyclic antidepressants are particularly lethal in overdosage, as their high tissue concentrations make removal difficult by standard treatments for overdose toxicity. Fortunately, the newer antidepressants are less toxic than the tricyclics. Among the newer antidepressants, overdose toxicity is an unimportant differentiation property, although tolerance and side effect profiles can be distinguishing characteristics.[14,15]

Stereochemistry

Stereochemistry is an increasingly important consideration in the development of drugs for clinical use. The most economical synthesis of drugs during the industrial "scale-up" process, which involves moving a laboratory-based procedure to the manufacture of the large quantities of drug needed for the commercial market, often results in racemic mixtures. A racemic mixture consists of isomers or enantiomers that are identical in chemical structure but differ in the orientation of atoms in space around a chiral center called an asymmetric carbon atom.[16] The importance of stereochemistry for the antidepressants lies in the recognition that isomers or enantiomers often show differences in their pharmacokinetic and pharmacologic properties.[17] Table 2 lists the relevant compounds for the newer antidepressants that exist in plasma in isomeric form.

Fluoxetine, citalopram, venlafaxine, mirtazapine, and reboxetine are administered as their racemic mixtures. Paroxetine and sertraline are both marketed as the most potent of their two isomers on serotonin reuptake inhibition. The potential advantages of drugs administered as single isomers include a less complicated pharmacokinetic profile, less potentially complex drug interactions, and a better probability for finding useful correlations between plasma drug concentration and clinical effects. An implication of choosing an antidepressant that is administered as a racemic mixture is that differences in patient response may be partially related to stereospecific metabolism. Currently, this is an infrequently-exercised criterion for choosing an antidepressant, as efficacy among the antidepressants is comparable in controlled clinical trials, and plasma drug concentration monitoring has not yet been demonstrated as clinically useful.

Fluoxetine serves as an example of an antidepressant with enantiomers that differ in pharmacologic potency. For example, the (R) and (S) enantiomers of fluoxetine are almost equipotent as serotonin reuptake inhibitors, but (R)-norfluoxetine is about 22 times less potent than (S)-norfluoxetine as an SSRI.[18,19] This means that the relevant compounds in plasma following administration of racemic fluoxetine for correlation with clinical effects are (S)-norfluoxetine and (S) and (R) fluoxetine. Of 12 published studies that have examined correlations between the plasma concentration of fluoxetine and its clinical effects, none have utilized measurements of the separate enantiomers of fluoxetine.[12]

A hindrance to the study of the physiological effects of individual drug isomers has been the availability of analytical methodology to separate these molecules. Because the individual isomers are nearly identical in many physical characteristics, resolution of individual isomers for quantification has been difficult, but recent advances in clinical chemistry now make this possible for all the antidepressants administered as racemic mixtures. Of obvious importance for a specific antidepressant is the issue of whether stereospecific metabolism has taken place. If liver enzymes preferentially metabolize one isomer more efficiently than another, then differences in pharmacologic effects between isomers may result in misleading conclusions when plasma drug concentrations are measured as total concentration and not individual isomers. Stereospecific metabolism has not been adequately studied for all the newer antidepressants. Table 2 reflects the potential importance of this property and the rigor that can be applied in future investigations to relate measures of antidepressant plasma concentration to their pharmacologic effects. The potential utility of finding strong correlations between plasma concentration and pharmacologic effect measures is to improve the number of responding patients among those given standard doses of antidepressants.

PHARMACODYNAMIC PROPERTIES

The overall clinical effects of an administered antidepressant result from both its pharmacokinetic and pharmacodynamic properties (Figure 1). Pharmacodynamic properties describe the effects of drugs on the body, while a drug's pharmacokinetic properties describe how the body

Table 3. Neurotransmitter Reuptake and Neuroreceptors Involved in the Actions of Antidepressants*

Drug	5-HT Reuptake	NE Reuptake	DA Reuptake	5-HT_{2A}	5-HT_{2C}	5-HT_3	α_1	α_2	Histamine$_1$
SSRI[a]	✔								
Bupropion		✔	✔						
Venlafaxine	✔	✔							
Nefazodone	✔			✔			✔		
Mirtazapine				✔	✔	✔		✔	✔
Reboxetine		✔							

*Abbreviations: 5-HT = serotonin; NE = norepinephrine; DA = dopamine.
[a]"SSRI" comprises fluoxetine, sertraline, paroxetine, fluvoxamine, or citalopram.

affects the drug.[7] Antidepressants display multiple pharmacodynamic properties (Table 1). Their effects on neurotransmitters and their receptor interactions have traditionally been assumed to reflect their mechanisms of antidepressant action. Recently, differences in effects on sleep architecture have been reported among some antidepressants. Most other pharmacodynamic properties relate to potential side effects.

Neurotransmitter and Receptor Effects

The major influence of antidepressants on CNS neuronal transmission results from direct inhibition of neurotransmitter uptake into presynaptic neurons or blockade or antagonism of various pre- and/or postsynaptic receptors.[1] The neurotransmitters most prominently involved are serotonin and norepinephrine. The major neurotransmitter uptake processes and receptors where the antidepressants act are summarized in Table 3. The mechanisms of action underlying therapeutic effects may involve various combinations of neurotransmitter and receptor effects. It is obvious that no single action or set of effects is exclusively involved in producing antidepressant effects.

Most of the newer antidepressants are known to exert either direct or indirect effects on the serotonergic (5-HT) system. The SSRIs are all potent inhibitors of 5-HT reuptake presynaptically. They bind with potent affinity to the 5-HT neuronal transporter, inhibiting the normal process of uptake into the presynaptic pool of neurotransmitters.[20] The rank order from most to least potent drug varies slightly among reports.[21,22] These inconsistencies appear to be due largely to differences in experimental methodology. It should be recognized that the relative in vitro potency only partially predicts the rank order of in vivo effects. The ultimate effect from a drug dose administered in humans is influenced by (1) pharmacokinetic variability in absorption, (2) distribution to the CNS, (3) the concentration achieved at receptor sites, and (4) the length of time that adequate concentrations are maintained at sites of action (Figure 1). This latter variable is strongly influenced by the efficiency of drug removal from the body, primarily by hepatic clearance. For example, although paroxetine appears to be more potent in vitro than fluoxetine as a 5-HT reuptake inhibitor, this minor difference is offset in vivo due to the longer half-life of fluoxetine and the production of an active metabolite with an even slower hepatic elimination.

It is paradoxical that antidepressants' inhibition of the reuptake of serotonin presynaptically may decrease the further release of serotonin. The increased extracellular concentration of serotonin in the synaptic space near serotonergic cell bodies in the raphe nuclei of the midbrain can activate somatodendritic autoreceptors of the 5-HT_{1A} subtype and suppress further release of serotonin.[23] This is an acute effect of the SSRIs, which normalizes within 14 days. Thus, while serotonin reuptake inhibition appears to underlie the ultimate antidepressant effects for most of the drugs in Table 3, this action may contribute to a delayed onset of action.

Recognition of the above neurochemical effects of the SSRIs has stimulated the use of pindolol as an adjunctive treatment for depression.[24] This β-adrenergic blocker possesses 5-HT_{1A} autoreceptor antagonist properties. By blocking the presynaptic 5-HT_{1A} autoreceptor, serotonin release is promoted even in the situation of increased synaptic 5-HT concentration from the presence of an SSRI. The use of pindolol has been shown in clinical trials[24,25] to have promising effects, perhaps hastening the onset of antidepressant response, but eventually producing no greater degree of response than an SSRI used alone.

In contrast to their high affinity for the 5-HT transporter, the SSRIs have low affinity for other neurotransmitter receptors, including α_1, α_2, histaminic$_1$, and muscarinic$_1$ receptors.[20,26,27] Paroxetine has measurable muscarinic$_1$ binding compared with the other SSRIs, but this binding level is substantially lower than that of the TCAs. Sertraline has more measurable dopamine receptor affinity than the other SSRIs. Such binding differences among the SSRIs may account for certain side effect differences, but the drugs' low affinity for receptors other than the 5-HT transporter accounts for a low degree of overall side effects.[14,15,28]

Nefazodone inhibits 5-HT reuptake but is also an antagonist at 5-HT_{2A} receptors and α_1 receptors.[29] Its potency for 5-HT_{2A} blockade is greater than the drug's potency for inhibiting 5-HT reuptake. The relevance of 5-HT_{2A} blockade by nefazodone is not completely clear. It is widely believed that enhancement of serotonergic neurotransmission underlies the therapeutic effects of many antidepressants; however, nefazodone results in a down-regulation of

5-HT_{2A} receptors in the brain, an effect counter-intuitive to the usual effects of an antagonist, which is to increase the sensitivity of a blocked receptor. One compensatory theory is that 5-HT_{2A} blockade results in an increased serotonergic neurotransmission by altering the function of 5-HT_{1A} auto receptors.[1]

Unlike the aforementioned drugs, the serotonergic effects of mirtazapine result not from reuptake inhibition, but rather from antagonism at pre- and postsynaptic 5-HT subreceptors.[30] In addition, by antagonizing α_2 receptors, the release of norepinephrine is stimulated, which becomes available for activation of α_1 receptors on serotonergic neurons. The net effect of mirtazapine's neurochemical actions is to increase serotonin neurotransmission.

Venlafaxine possesses 5-HT reuptake inhibitory effects and, in addition, inhibits the reuptake of norepinephrine.[31] This latter property was inherent in the action of several TCAs; however, venlafaxine does not share the side effect liability of this older group of drugs.

It is apparent that a serotonergic effect is not an absolute prerequisite for a drug to be an effective antidepressant (Table 3). Bupropion appears to have marginal effects on serotonin. Its primary pharmacologic effect has been previously thought to involve the reuptake inhibition of dopamine.[32] A more recent interpretation of the data implicates norepinephrine involvement in its pharmacologic actions. Another exception to the prerequisite of 5-HT effects for antidepressant activity is reboxetine, an antidepressant marketed in Europe and of investigational status in the U.S.[33] Reboxetine has been shown in placebo-controlled clinical trials[33,34] to have antidepressant effects, and its predominant neurochemical effect involves norepinephrine reuptake inhibition.

SSRIs are widely regarded as the drugs of first choice for patients who need treatment with antidepressants. However, controlled clinical trials[35] consistently show that the rate of nonresponse to SSRIs varies between 20% and to 40%. Thus, many patients will require an alternative or adjunctive treatment. When a patient does not respond adequately to an SSRI as the first antidepressant, the question arises of whether a second SSRI should be substituted or a new antidepressant chosen with a different mechanism of action. There is no overwhelming evidence that any particular combination of neurotransmitter or neuroreceptor effects is any better than another as a desirable mechanism of antidepressant effect. Direct comparisons of newer antidepressants in clinical trials using[36,37] parallel group design are not convincing concerning the superiority of one drug over another in terms of treatment efficacy. Given the array of available drugs (Table 3), a cogent argument can be made for trying a second agent with a different overall effect on neurotransmission. Of course, dose, length of previous treatment, the availability of adjunctive psychotherapy, and other considerations are important when making a decision to switch antidepressants.

Table 4. Antidepressant Effects on Sleep Parameters*

Drug	Continuity	SWS	REM	Sedation
SSRI[a]	No change or decrease	No change or decrease	Decrease	No significant effect
Bupropion	Decrease	No change	Increase	No significant effect
Venlafaxine	ND	ND	Decrease	Moderate effect
Nefazodone	Increase	No change	Increase	No significant effect
Mirtazapine	Increase	Increase	Decrease	Moderate effect
Reboxetine	No change or decrease	ND	ND	No significant effect

*Adapted from references 38–40. Abbreviations: SSRI = serotonin selective reuptake inhibitors; SWS = slow wave sleep; REM = rapid eye movement; ND = no data available.
[a]Complete data are unavailable for all SSRIs but are presumed to show minor differences.

Effects on Sleep

Sleep studies[38–40] suggest that the differential pharmacology of the newer antidepressants is reflected in the effects on sleep parameters. There are few direct comparisons between antidepressants concerning effects on sleep parameters in depressed patients, although sleep effects have been studied for most newer drugs, either in open label studies or against placebo. The effects of the commonly used antidepressants and reboxetine are summarized in Table 4.

In laboratory sleep studies, the SSRIs have caused a depression in REM (rapid eye movement) sleep and an increase in REM latency. These effects either are insignificant or contribute to disturbed sleep patterns in normal healthy volunteers. A recent study[38] demonstrated differences in the sleep effects of fluoxetine in comparison with nefazodone. Differences emerged in REM latency and Stage 1 sleep. It is well recognized that sleep complaints improve with the clinical improvement in overall depressive symptomatology with most antidepressants; however, specific complaints may be amenable to treatment with one or another of the drugs listed in Table 4. The differences in effects on sleep architecture that have been reported among the antidepressants are of doubtful significance as mechanisms of antidepressant action; however, they may have an impact on patient acceptance of drug therapy and on quality of life.

Cardiovascular Effects

The newer antidepressants have minimal direct effects on cardiovascular functioning.[41] Serotonin modulates vascular resistance in a complex manner, and reports of cardiac arrhythmias with the SSRIs might be expected; however, given the millions of patients exposed to these drugs, an association with untoward cardiac events is practically nonexistent. Most new antidepressants have been shown to have only marginal effects on heart rate and blood pressure, although orthostatic hypotension, which may be exacer-

Table 5. Reported Pharmacokinetic Parameters of Newer Antidepressants*

Drug (active metabolite)	Bioavailability (%)	Plasma Protein Binding (%)	Volume of Distribution (L/kg)	Clearance (L/h)	Half-Life (h) Mean (h)	Half-Life (h) Range (h)	Average Steady-State Plasma Concentration (ng/mL)
Fluoxetine	80	95	25	10–36	45	24–144	90–300
(Norfluoxetine)	…	…	…	…	…	200–223	70–260
Sertraline	> 44	98	25	96	26	22–36	20–200
(Desmethylsertraline)	…	…	…	…	71	62–104	> parent concentration
Paroxetine	> 64	93	17	36–167	18	7–65	10–600
Fluvoxamine	> 53	77	> 5	80 (33–220)	15	9–28	20–500
Citalopram	95	82	14	26 (23–38)	33	23–45	40–300
Bupropion	90	80	27–60	116–362	10	4–23	5–50
(Hydroxybupropion)	…	…	…	…	21	…	200–1500
Venlafaxine	92	27	2–23	40–129	…	2–11	50–150
(O-desmethyl)	…	30	9–13	…	…	6.5–16	200–400
Nefazodone	> 20	99	0.2–1.0	…	…	2–8	150–1000
Mirtazapine	50	85	4.5	…	…	13–34	20–40
Reboxetine	> 60	97	0.5	1.7	…	12–16	50–160

*Data from references 12, 17, 42, and 47.

bated by many drugs, can be a problem in the elderly. Venlafaxine can cause a dose-dependent increase in blood pressure, which should be monitored in all patients receiving this antidepressant.[42] For patients who are receiving other pharmacotherapy, the potential for antidepressants to participate in drug-drug interactions with cardiovascular drugs may be an important consideration when selecting treatment.

Effects on Psychomotor Function

The SSRIs have minimal effects on psychomotor function in comparison with other psychoactive drugs, such as the benzodiazepines. The effects of paroxetine have been extensively tested in driving simulations and other paradigms.[43] The majority of studies show little or no effect on psychomotor function or behavioral toxicity. In tests of their effects in combination with alcohol, the newer antidepressants also show minimal psychomotor impairment. Given a lack of enhanced impairment when combined with alcohol, the SSRIs have been used for treatment of alcoholism with some success.[44]

Related to psychomotor function is the issue of neurologic syndromes produced by the newer antidepressants. Extrapyramidal symptoms including parkinsonism, dystonia, and akathisia have been associated with the SSRIs, although the data suggest the incidence is very low.[45] The majority of cases have been reported in association with fluoxetine, but this is to be expected as this antidepressant has received the most patient exposure. There is a lack of epidemiologic data to compare the various new antidepressants for their propensity to produce this rare side effect.

PHARMACOKINETIC PROPERTIES

Pharmacokinetic properties describe the way in which the body responds to the administration of a drug. Some pharmacokinetic properties of the newer antidepressants are summarized in Table 5.

Absorption and Elimination

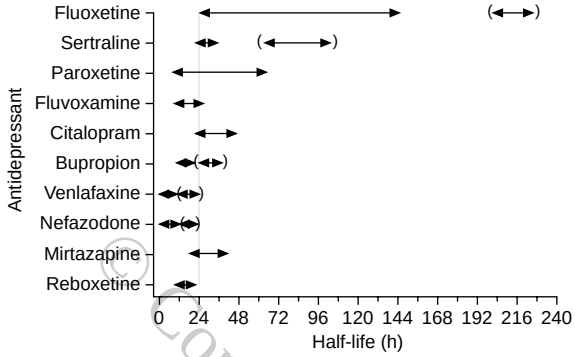
The orally administered antidepressants are absorbed into the circulation and distributed to sites of action where they produce pharmacodynamic effects. The body's physiology reacts to the presence of an antidepressant as it would to the invasion of the body by any outside chemical. Various mechanisms are available for drug elimination. Cytochrome enzymes in the gut wall and liver metabolize part of the antidepressant dose before it reaches the systemic circulation. This produces relatively low values for bioavailability, seen in Table 5. The favorable lipid and water solubility of the antidepressants, as discussed earlier, results in a rapid, although passive, diffusion of drug into the circulation. At the time point when the rate of absorption is balanced by the rate of distribution and/or elimination from the circulation, a maximum concentration in plasma is reached. This time varies between the antidepressants and is influenced by the presence of food.

Most drugs are eliminated by multiple pathways. Drugs can be biotransformed to one or more metabolites and a proportion of the dose is usually excreted unchanged. Conditions which can alter the pathways of elimination include physiological conditions, aging, and genetic polymorphism, in addition to drug-drug interactions. The significance of these variables altering the dose-effect relationship will depend upon the importance of the pathway to the overall elimination of the drug, the activity of various metabolites, and degree to which plasma concentrations are altered from the normal. The set of pharmacokinetic properties is only one of several important variables to consider in the choice of an antidepressant (Table 1).

Distribution

Most of the antidepressants are highly bound to plasma proteins. This presumably serves to keep the drugs in the circulation, so that they can be eliminated via blood flow

Figure 2. Reported Ranges of Elimination Half-Lives for Newer Antidepressants*



*The double arrow for each drug refers to parent drug half-life, and arrows in parentheses show metabolite half-life. The broken line denotes the value of 24 hours.

to the liver; however, avid tissue binding results in extensive drug distribution to various organs, including the brain. Such broad distribution in the body, indicated by a high volume of distribution, is balanced by effective removal by the liver. The combination of a high volume of distribution and high hepatic clearance results in half-lives for most of the antidepressants in the range of 12 to 24 hours, which is convenient for once-daily dosing. A few exceptions are found.

Metabolism. The ranges of half-life values reported for new antidepressants are displayed in Figure 2 so that the relative values and variability among the drugs can be appreciated. The value of 24 hours is noted due to its significance for daily drug dosing. When a drug with a half-life of this length is dosed once daily, 50% of the total amount of drug in the body will be removed and replaced each day. The differences in half-life translate into clinical differences among the drugs. The short half-lives of bupropion, venlafaxine, and nefazodone requires that they be administered in multiple daily doses. This shortcoming of their pharmacokinetic properties can be overcome by formulation as a sustained-release product for oral administration. This generally results in more convenient dosing. For venlafaxine, administration in a sustained-release formulation has been shown to be as efficacious as multiple daily dosing and to have a better side effect profile.[46] Unfortunately, because of the more complex manufacturing technology involved, sustained-release products are frequently more expensive than drugs formulated as immediate-release products.

Fluoxetine and its active metabolite display the longest half-lives among the antidepressants. This characteristic can be an advantage and a disadvantage. A drug with a long half-life is an advantage for patients who are in remission from depression and occasionally do not take a daily dose. Because of the long half-life and slow clearance of fluoxetine, missing a daily dose will have less of an impact on the loss of total drug in the body than would missing a dose of antidepressants with shorter half-lives. Fortunately, missing a single dose of any of the antidepressants is unlikely to result in the immediate return of depressive symptoms, but continual low compliance during maintenance treatment poses a mental health risk for all of the drugs. A disadvantage for fluoxetine due to its long half-life and that of its active metabolite is the prolonged washout period that occurs once the parent drug is discontinued. This property results in pharmacologic effects persisting longer after stopping drug dosing, in comparison with the other antidepressants. Thus, a monoamine oxidase inhibitor should not be started until 5 weeks after fluoxetine is discontinued.[47] Also, the effects of hepatic enzyme inhibition can persist for weeks after fluoxetine is stopped.[47,48]

Another issue that partly relates to an antidepressant's half-life is the discontinuation syndrome. Withdrawal symptoms commonly appearing after discontinuation of SSRIs have included dizziness, fatigue/weakness, nausea, headache, myalgias, and paresthesias.[49–51] These withdrawal reactions have been reported with all SSRIs. The long half-life of fluoxetine has been suggested as a self-tapering mechanism that prevents the discontinuation syndrome, but in fact, the syndrome may still appear with fluoxetine—just longer after discontinuation than with other SSRIs. Therrien and Markowitz[49] found that the length of time for the appearance of discontinuation symptoms was 6.4 days after fluoxetine was stopped, compared with 2 to 4 days for fluvoxamine, sertraline, and paroxetine. The likelihood of a discontinuation syndrome occurring appears related to the length of treatment and possibly to drug potency and other factors, in addition to half-life. Without accurate prevalence data, it is difficult to conclude that a discontinuation syndrome occurs more often with one drug than another. Ratings of severity for comparing the withdrawal of one SSRI to another are generally absent from the literature but many experts feel the syndrome is mild, disappears, and is preventable by tapering the dosage as an SSRI is stopped. No specific treatment is recommended beyond reinstitution of the antidepressant, with subsequent gradual tapering as tolerated.

Interactions With Drug-Metabolizing Enzymes

The interaction of the newer antidepressants with hepatic cytochrome P450 enzymes that metabolize many drugs has been a field of extensive investigation. An improved understanding of oxidative drug metabolism, particularly regarding the complexity of the P450 family of enzymes, has strengthened knowledge of the scientific basis of drug interactions. Two enzymes in particular, cytochrome P450 2D6 and 3A4, together appear to be responsible in part for the metabolism of over 80% of the therapeutic drugs on the market. Thus, a drug's ability to inhibit or induce these enzymes may be clinically mean-

Table 6. Newer Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential*

	CYP Enzyme			
Drug	1A2	2C	2D6	3A4
Fluoxetine	0	++	++++ (++++)	++ (++)
Sertraline	0	++ (++)	+ (++)	+ (+)
Paroxetine	0	0	++++	0
Fluvoxamine	++++	++	0	+++
Citalopram	0	0	0	0
Nefazodone	0	0	0	++++
Venlafaxine	0	0	0 (+)	0
Bupropion	0	0	0	0
Mirtazapine	0	0	0	0
Reboxetine	0	0	0	0

*Data from references 52–57. The effect of a metabolite is shown in parentheses. Symbols: 0 = unknown or insignificant; + = mild and usually insignificant; ++ = moderate and possibly significant; +++ = moderate and usually significant; ++++ = potent.

ingful when polypharmacy occurs during the treatment of depression.

Table 6 summarizes the potential of the newer antidepressants to competitively inhibit some P450 enzymes. This table was constructed as a synthesis of the published in vitro data,[52–57] which considers drug affinity for specific isozymes, clinical case reports of interactions, and human pharmacokinetic studies. Additional factors beyond enzyme affinity will play a role in determining the clinical significance of an in vivo drug interaction. These have been discussed extensively in the literature.[52,58,59]

Drug names: amoxapine (Asendin), bupropion (Wellbutrin), clozapine (Clozaril), dopamine (Dopastat, Intropin), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), mirtazapine (Remeron), nefazodone (Serzone), norepinephrine (Levophed), paroxetine (Paxil), pindolol (Visken), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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Disclosure of Off-Label Usage

The following agent mentioned in this article is not indicated for adjunctive treatment of depression: pindolol.

The following agents mentioned in this article are not indicated for treatment of alcoholism: SSRIs.