Classification of Antidepressants and Their Clinical Implications

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Preclinical and clinical data provide information pertinent to the potency, efficacy, safety, and tolerability of antidepressant medications. Such data may serve as the basis of informed clinical decisions based on a rational approach to drug selection that is tailored to the patients' needs. This article reviews comparative data on the binding potencies of antidepressants to receptors and transporters of serotonin and norepinephrine as well as physiologic measures of the effects of these drugs in humans.
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Since the rise of "first-generation" antidepressants, the tricyclics and monoamine oxidase inhibitors, introduced in the late 1950s, the number of new classes of antidepressant medication used to treat major depressive disorders has grown dramatically. Newer classes of drugs include the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), dopamine-norepinephrine reuptake inhibitors, serotonin modulators, norepinephrine-serotonin modulators, and selective norepinephrine reuptake inhibitors (NRIs). The introduction of these newer classes has significantly transformed the pharmacologic treatment of depression. Compared with traditional antidepressant drugs, newer drug classes such as SSRIs and SNRIs offer improved tolerability to therapy with a high level of efficacy. Yet, some patients may not benefit from initial treatment with a given drug class due to the side effect profile or a less than adequate response to therapy. With a better understanding of how drugs are classified, more appropriate treatment decisions may be made in order to determine the most suitable drug for a given patient.

The classification of antidepressant drugs is based largely on their mechanisms of action; however, this is only one part of the drug selection process. Other important considerations include issues such as safety, efficacy, tolerability, and formulation. Therefore, it is important to take into account not only the drug classification, but also other clinical features of a drug. This approach should be helpful in determining the drug most likely to be of benefit to the patient, particularly when a physician is faced with clinical challenges such as failure of first-line treatment or cases in which a combination of treatments is warranted. This article will briefly review how the antidepressant properties of a drug are qualified and quantified and, consequently, how drugs with similar characteristics are classified according to their mechanism of action and, finally, how such classifications can help guide rational treatment decisions.

THE PHARMACOLOGIC EFFICACY OF A DRUG

Drugs may be classified by their origin or source, by physiologic effects, therapeutic use, site of action, chemical structure, or mechanism of action.[1] While it may seem logical to classify drugs by their chemical structure (e.g., tricyclic antidepressants), such a classification system does not provide a meaningful way of categorizing the effects of the drug. In the case of newer antidepressants (e.g., SSRIs, SNRIs), the means of classification generally has been the purported mechanism of action, offering more useful information to the clinician than classification based on structure.

In general, pharmacologic effects are a function of the drug's actions directly on target proteins (e.g., receptors) or changes effected by the drug's action at these sites. Adverse effects typically result from additional (unwanted) effects of the drug's action at these targets and any additional (generally unintended) binding sites. More specifically, the effect of a drug is based on the number and nature of the binding sites that recognize the drug, the

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Table 1. Comparisons of the Effects of Serotonin and Norepinephrine

Serotonin regulates
Sleep
Mood
Appetite
Sensory (ie, pain) transmission
Autonomic response
Endocrine function
Norepinephrine regulates
Arousal, attention, and concentration
Energy, motivation, and pleasure (hedonic response)
Blood pressure
Appetite

concentration of the drug at these sites, and whether the drug functions as an agonist or antagonist. Therefore, one way of looking at a drug's pharmacologic properties is to determine how effective it is in eliciting a cellular effect once it has interacted with its target.

How a drug recognizes and interacts with its receptor or transporter helps to determine its activity and efficacy. A drug may directly act on a receptor as full or partial agonist or block the binding of other substances at this site (i.e., a receptor antagonist).

Drugs such as SSRIs and SNRIs produce their effects on the central nervous system via their actions on synaptic transmission. In general, these drugs work on a very limited number of transmitters, including catecholamines (dopamine and norepinephrine), serotonin (5-hydroxytryptamine [5-HT]), and acetylcholine.

Drugs that exert their action via 5-HT pathways affect 5-HT–containing neurons that are located in the brainstem (pons and medulla), primarily the raphe nuclei. Serotonin neurons project into the neocortex, limbic system, hypothalamus, and cerebellum. There are at least 14 5-HT receptor subtypes. Because 5-HT receptors are found to be important for sleep, mood, motoneuron function, sensory transmission, and autonomic functions, a drug that acts on a 5-HT receptor can affect sleep, mood, pain, movement, and endocrine function (Table 1). The therapeutic effects of SSRIs stem (predominantly) from their inhibition of the reuptake of serotonin via blockade of the high-affinity serotonin transporter (also know as a reuptake site).

Norepinephrine (NE)-containing neurons are located in the same region as 5-HT–containing neurons—the pons and medulla of the brainstem. There are at least 11 NE receptor subtypes, although most of the effects are associated with 2 subfamilies, the α and β_1 receptors. Norepinephrine is associated with a broad range of effects, including effects on attention, appetite, reinforcement, mood, arousal, and blood pressure regulation. While both SSRIs and SNRIs elevate the synaptic levels of 5-HT, SNRIs also elevate synaptic levels of NE.[2] Therefore, in theory, an antidepressant classified as an SNRI should be able to affect the processes linked to the hallmark symptoms of depression associated with the function of 5-HT, such as depressed mood and sleep disturbances, as well as the areas of the brain associated with attention, arousal, and motivation linked to NE (and, indirectly, dopamine). The next section summarizes how these actions translate into neurophysiologic effects.

THE CLASSIFICATION OF A DRUG

Preclinical studies provide much of the information necessary to classify a drug. In addition, the results of these studies can offer explanations for the potency, efficacy, safety, and tolerability of the antidepressant medications observed in subsequent clinical trials. Most preclinical studies of antidepressants are attempts to gain insight into the effects of the drug in relation to the functioning of the brain by investigating the drug either in a laboratory or other artificial environment outside the body (in vitro) or in the living body of an animal (in vivo). Because preclinical studies are performed in isolation, they offer the advantage of limiting other, possibly confounding study variables during drug evaluation. The results of these studies are then considered together with studies in humans to better understand overall drug function and activity. For the purposes of this review, the methods used to qualify and quantify the pharmacologic effects of antidepressants are discussed using the example of SSRIs and SNRIs to describe the process leading to classification of these agents on the basis of the mechanism(s) of action exhibited at this level of investigation.

In Vitro Studies

In vitro studies evaluating the properties of SSRIs and SNRIs look at how the drug binds to the receptor (via receptor binding assays), the drug's effect on reuptake, and the relative effect of the drug on different receptors (selectivity) in an effort to determine the mechanisms of action responsible for the antidepressant properties observed in preclinical models and clinical trials and the potency of a particular agent (and hence the concentration required for it to exert the given effect at the site of action).

Binding assays. Binding studies are used to determine the ability of a drug to attach to a particular site (affinity) and can be performed in native tissue or an in vitro cell preparation. Drug binding is evaluated at various drug concentrations. The amount of drug that is bound to the receptor is determined by adding a radioactive chemical tag to these receptors. A drug with a high affinity for a receptor will tend to displace a larger amount of the tag, resulting in a lower value. The binding affinity is generally depicted as an inhibition constant (K_i) and expressed in molar concentrations (i.e., nanomolar, micromolar). Because the K_i is measuring inhibition of the binding of the tag, a more "tightly" bound drug has a lower K_i value.

Table 2. Relative Binding Affinity (K_i, in nM) of Antidepressants for the Serotonin Transporter (reuptake site) and Norepinephrine Transporter[a]

	Serotonin Transporter		Norepinephrine Transporter	
Drug	Rat	Human	Rat	Human
Paroxetine	0.05	0.065	59	85
Sertraline	0.29	0.15	1597	817
Citalopram	0.75	1.5	3042	7865
Fluoxetine	2.0	0.9	473	777
Imipramine	8.7	1.3	11	20
Amitriptyline	16	2.8	8.6	19
Venlafaxine	19	7.5	1067	2269
Nortriptyline	60	15	0.99	1.8
Desipramine	129	22	0.31	0.63
Nefazodone	220	459	555	618

[a]Data from Owens et al.[3]

Information derived from receptor binding assays can be used to determine and compare the affinity of different antidepressants for a given binding site (e.g., how tightly each drug binds to a receptor or transporter). These studies also show whether a drug can act on more than one receptor and if it can interfere with the action of other drugs on each receptor. In some cases, a drug can have different effects depending on the tissue type or cell source (i.e., species of origin).

Currently available antidepressants exhibit a wide range of affinities for NE and 5-HT transporters as shown in a comprehensive assessment by Owens and colleagues[3] of the binding of drugs to the serotonin transporter (SERT) and norepinephrine transporter (NET) (Table 2). Again, because low K_i implies a high affinity, a drug such as desipramine (0.63 nM) has a much higher affinity for NET than fluoxetine (777 nM), while paroxetine (0.065 nM) has a higher affinity for SERT than nefazodone (459 nM). With this in mind, however, receptor binding is only the first step in understanding overall pharmacologic effects. Other factors such as drug availability and solubility must also be considered.

Uptake. In addition to measuring the affinity for a transporter, the effects of a drug on inhibiting uptake of a neurotransmitter can be measured in order to estimate relative drug potency. In this case, *potency* usually refers to the concentration or dose of a drug necessary to elicit a specific effect. For example, a response such as a behavior (e.g., seizure) can be tested against one or more drug doses to find the dose-response relationship as well as the effective concentration (EC_{50}) or effective dose (ED_{50}) required to produce 50% of the maximal effect. This same strategy is used to measure the potency of inhibiting uptake of a transmitter.

For in vitro uptake studies, dispersed cells, synaptosomes, or tissue slices are incubated in the presence of a radiolabeled tag that can be taken up by the transporters of interest (e.g., NET incubated with [^{3}H]NE). By counting the radioactivity after incubation, the amount of transported tag can be estimated. The drug of interest is then added to the preparation to determine its effects on transport. A drug with a lower EC_{50} is considered to have higher potency.

Both binding and uptake studies can also be performed using cell lines that have been transfected with a human receptor or transporter of interest. The advantage of using transfected cell lines is that only the activity of that single receptor is measured without the confounding interactions of other receptors or transporters.

Selectivity. *Selectivity* refers to the relative binding affinity or potency of a drug for 2 different sites, expressed as a ratio. For example, the selectivity of an antidepressant for binding to NET over SERT would be expressed as (K_i for NET)/(K_i for SERT). The same calculation may be made by evaluating potency at one site (i.e., inhibiting uptake) using the EC_{50} values or [^{3}H]NE uptake via NET.

The important question, however, is whether selectivity is clinically relevant. In other words, is there a meaningful difference between a drug that has a 500- versus a 50-fold selectivity for NET or SERT? In general, information about selectivity for 5-HT or NE is relevant only when it can be demonstrated in vivo, and the drug must have sufficient receptor affinity to exert a therapeutic effect at the doses used in clinical practice. A drug may be highly selective for a particular receptor, yet exhibit no therapeutic effect clinically. Alternatively, when a drug has a much higher affinity for one site, effects at the lower-potency site are not precluded.

Drugs with high affinity for a binding site will eventually saturate the site. Therefore, testing for selectivity is meaningful only when drug doses below saturation are used. In fact, selectivity is not considered a very good predictor of clinical effects, because drug doses in vivo are often above saturation concentration.[4] This is why some drugs with a higher affinity for SERT than for NET may continue to show NE-type clinical effects in the absence of additional clinical 5-HT effects as drug dosages are increased in the patient; that is, the drug saturates the higher affinity site at lower doses; the binding to the second site, then, increases as the dose goes up. Eventually, if the dose is high enough, the drug may attain nearly complete binding to both sites, yielding an effective ratio of 1:1.

In Vivo Studies

In vivo study of drug administration on the peripheral and central nervous system helps establish the selectivity and potency of a drug's effects observed in vitro. Techniques used include electrophysiologic measurements and physiologic challenges in animal models and human subjects (e.g., the tyramine pressor response test, vasoconstriction pressor test, and platelet 5-HT uptake test). Because these tests measure the peripheral action of a drug, they do not completely describe the mechanisms of action of a study drug on the central nervous system. Therefore,

these studies are used to infer central effects and help confirm in vitro mechanisms of action.

Electrophysiologic experiments. Electrophysiologic experiments indirectly measure the relative potency of a drug in vivo and are used to correlate in vitro findings.[5] For example, drugs that act as NET inhibitors increase the synaptic availability of NE, which activates presynaptic α_2-receptors and produces the acute inhibition of the firing of NE neurons, such as those in the locus ceruleus. The reduced firing of locus ceruleus neurons indicates that NET is inhibited.[6] Likewise, drugs that inhibit the uptake of the 5-HT transporter increase the amount of 5-HT available to act on autoreceptors (e.g., 5-HT_{1A}) and reduce the firing of neurons in the dorsal raphe nucleus. The reduced firing of raphe neurons indicates that SERT is blocked.[6]

For most psychotropic agents, in vivo studies correlate well with in vitro findings, although there are exceptions to this rule. Venlafaxine, for example, exerts much more potent effects in vivo than would be predicted from its in vitro affinity for NET and SERT. This has been attributed in a large part to its distinctly different pharmacokinetic profile (discussed in the next section) and the high availability of its active metabolite O-desmethylvenlafaxine. Therefore, while another serotonergic agent, such as paroxetine, might exhibit a much higher in vitro affinity for SERT, both inhibit with similar potency the firing of 5-HT neurons in the rat dorsal raphe.[5] Similarly, while venlafaxine has a low NET binding potency, it fully inhibits NE neuronal firing in the locus ceruleus.[5] Ongoing studies are investigating whether this SNRI acts on other receptors and neuronal pathways that may also account for this effect.

Tyramine pressor test. The tyramine pressor test is considered a reliable measure of peripheral NE response to NET blockade. Normally, tyramine is taken up into nerve terminals via NET. There it is taken up into vesicles, displacing NE into the synapse. With release of NE, there are mild and transient increases in blood pressure (mediated via α_1-receptor stimulation) that can be measured.[7,8] When a drug such as a selective NRI or an SNRI blocks NE uptake, tyramine uptake is reduced and there is less increase in blood pressure. The action of a drug on NET blockade is evaluated by comparing blood pressure changes before and after drug treatment.[7,8]

As would be expected, the SSRI paroxetine at a dose of 30 mg/day displays no effect on norepinephrine when such a test is used.[9] Alternatively, a study of healthy male volunteers comparing the SNRI venlafaxine (375 mg/day and 75 mg/day), the SSRI sertraline (50 mg/day), and the selective NRI maprotiline (150 mg/day) showed that the SNRI venlafaxine at a dose of 375 mg/day and the selective NRI maprotiline at 150 mg/day were both able to blunt the pressor response to tyramine, thereby indicating that they block uptake of NE in humans.[7]

Vasoconstriction pressor test. This test measures a peripheral NE response by evaluating a drug's effect on blood flow in the dorsal vein of the hand. It relies on the fact that any NE agonist as well as NE reuptake inhibitor will cause peripheral vasoconstriction. NE reuptake inhibitors also produce vasoconstriction by increasing synaptic transmission of NE. Drugs such as desipramine at a dose of 100 mg/day and venlafaxine at a dose of 150 mg/day both enhance vasoconstriction because they block peripheral NET.[10] Not surprisingly, paroxetine at a dose of 20 mg/day does not elicit vasoconstriction.[10] Interestingly, venlafaxine at 75 mg/day also exerted no significant vasoconstriction response.[10]

Pupillary light reflex response test. The previous tests are peripheral measures of noradrenergic effects. Because the agents evaluated are centrally acting drugs, evaluations of central activity provide a particularly relevant means of measuring the NE action of such agents. This test measures the central NE response of the pupil to light. Because the resting pupil diameter is established by both sympathetic (NE) and parasympathetic (muscarinic cholinergic [mACh]) activity, an increase in NE or a decrease in mACh activity increases the resting pupil diameter. In a study that evaluated the pupillary light reflex response to doses of venlafaxine (75 and 150 mg/day), desipramine (100 mg/day), and paroxetine (20 mg/day),[11] neither desipramine nor paroxetine was able to change pupil diameter, while both doses of venlafaxine did increase pupil diameter. Because of the inability of desipramine to evoke a response, the study is difficult to interpret, although the effect may have been inhibited as a result of the α_1 receptor block by desipramine. In other words, the balance between the mydriasis resulting from norepinephrine uptake blockade and the miosis from α_1 receptor blockade might have yielded the net effect of no significant change in pupil diameter observed with desipramine in this experiment. Nonetheless, the study does illustrate that the SNRI venlafaxine at doses of 75 mg/day and 150 mg/day is able to evoke a central NE response, while an SSRI is unable to evoke such a response.

Platelet 5-HT uptake test. This test measures a drug's effect on the uptake of 5-HT into human platelets. Because SSRIs can block uptake, they are expected to exert an effect, while drugs from other drug classes lacking 5-HT receptor effects should exhibit little or no effect. In fact, sertraline and venlafaxine were found to significantly inhibit platelet 5-HT uptake, while maprotiline had no effect.[7]

Pharmacokinetic Factors

When extrapolating the results of preclinical studies to the clinical setting, it is important to consider pharmacokinetic factors, such as drug metabolism, protein binding, and lipid solubility, which, together, determine the degree to which a drug will cross the blood-brain barrier. Orally

administered drugs are absorbed from the gastrointestinal tract into the systemic circulation, where they undergo first-pass metabolism in the liver and eventually gain access to brain receptor sites by crossing the blood-brain barrier. Drugs with high lipid solubility and low protein binding are available at higher concentrations in the central nervous systems than those with lower lipid solubility or higher protein binding.[12]

Most SSRIs are highly protein bound with only 2% to 10% circulating in an unbound form.[13] Other drugs have considerably lower protein binding; for example, venlafaxine has less than 30% protein binding.[14] Because the absolute degree of binding of a drug is determined by both its affinity for a binding site and the amount delivered to the site, the low protein binding of venlafaxine enhances its availability at its site of action. This may well explain why it has a therapeutic effect in spite of a lower absolute in vitro SERT and NET binding affinity than SSRIs. Paroxetine, an SSRI with high binding affinities for both SERT and NET, is 95% bound by protein, accounting for the fact that the concentration of paroxetine in the central nervous system (i.e., concentration in cerebrospinal fluid) is less than 4% of what is measured in the plasma.[15]

Another related factor influencing the amount of drug that is available at its site(s) of action is the relative plasma level, which is in part determined by dosage. This is an important consideration particularly when comparing the in vitro actions of one agent versus another and attempting to interpret the clinical relevance of the findings. For example, drug X might exhibit a 5-fold greater affinity for a particular receptor than drug Y, but if the dose of drug Y is 10 times that of drug X (e.g., 100 mg vs. 10 mg), drug Y may, in fact, exhibit greater effects at that receptor clinically.

DISCUSSION

The above studies illustrate the methods used to study the effects of antidepressants at their sites of action, and, in the case of SSRIs and SNRIs, to classify the agents accordingly. While the choice of initial therapy must be individualized for each particular patient on the basis of multiple factors, such as presenting symptoms, treatment history, sensitivity to potential side effects, and concomitant disease states and medications, an understanding of the mechanism of action of antidepressants can be important for optimizing treatment of depressive episodes, particularly when selecting augmenting strategies or combining therapies. The mechanism of action of an antidepressant should also be considered when switching to another agent after failure of initial therapy. In these situations, it is important to consider the site of action of the agents in question in order to promote pharmacologic synergy and minimize tolerability issues. For example, combining agents such as desipramine and fluoxetine[16] might yield a better therapeutic outcome than fluoxetine and another predominantly serotonergic agent. Furthermore, switching from one SSRI to another makes little pharmacologic sense.

CONCLUSION

While mechanism of action alone can neither predict nor account for the full clinical benefit of any one drug, it provides clinicians with an initial understanding of how the drug is expected to behave. Additional factors, such as a drug's pharmacokinetic profile (lipid solubility, protein binding, and ability to cross the blood-brain barrier), that influence its availability at the synapse are equally important and greatly influence the activity of a drug. Despite study limitations, however, the results of the in vitro and in vivo investigations described above do more than simply provide theoretical explanations for observed clinical benefits. The information afforded by these studies helps us to further refine our understanding of how and why drugs work. In combination with clinical data, such an approach can be a powerful tool for making rational decisions about therapy.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), maprotiline (Ludiomil and others), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), tyramine (Questran, Cholestyramine, and others), venlafaxine (Effexor).

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