Interactions of Antidepressants With Neurotransmitter Transporters and Receptors and Their Clinical Relevance

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This review discusses the pharmacology of antidepressants as it relates to their blockade of human transporters for norepinephrine, serotonin, and dopamine, as well as their blockade of several different human neurotransmitter receptors. This blockade by antidepressants of transporters and receptors is thought to relate to therapeutic and adverse effects of these compounds. Knowledge of the preclinical pharmacology of antidepressants will help the clinician to identify adverse effects and drug interactions that may occur with these agents. The article also reviews drugs that have dual action (effects on serotonin and norepinephrine), which may provide a therapeutic advantage in treating depressed patients. *(J Clin Psychiatry 2003;64[suppl 13]:5–12)*

In the United States today, there are over 20 different drugs approved by the U.S. Food and Drug Administration (FDA) to treat depression. More than half of these compounds have been available for decades. The evolution of the development of drugs for the pharmacotherapy of depression has been that drugs with a multiplicity of effects (e.g., tricyclic antidepressants) have been superseded by those with selective actions (i.e., serotonin selective reuptake inhibitors [SSRIs]). This evolution came about to reduce adverse effects of antidepressant drugs, by largely eliminating interactions with certain neurotransmitter receptors. Although these more selective compounds may be better tolerated by patients, there is increasing evidence to suggest that selective drugs, specifically SSRIs, do not yield superior efficacy as measured by response and remission rates in treating depressed patients. In fact, it may be an advantage to increase synaptic levels of both serotonin and norepinephrine, as, for example, with venlafaxine (at high dosages) and with the new antidepressant duloxetine. Since knowledge of the pharmacology of antidepressants can help the clinician in the selection and use of these agents, this review will present some of their pharmacology as it relates to their effects at synapses in the brain, as well as elsewhere in the body. The information presented from preclinical studies will show how these effects may relate to the therapeutic and adverse effects of these compounds and why some antidepressants are more likely than others to cause these effects. Thus, the reader will learn what might be the clinical relevance of the effects of antidepressants on specific neurotransmitter systems.

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THE SITE OF ACTION OF ANTIDEPRESSANTS IS THE SYNAPSE

Whether therapeutic or adverse, most of the effects of antidepressants in the body occur at the level of the synapse, where one neuron communicates with another neuron or another type of cell (e.g., smooth muscle cell). By either blocking neurotransmitter transport, blocking certain neurotransmitter receptors, or inhibiting the mitochondrial enzyme monoamine oxidase, antidepressants change the magnitude of the effects of neurotransmitters at these synapses. Some biogenic amine neurotransmitters, after release, are taken back into the nerve ending. Reuptake occurs through transport proteins (transporters), which have been molecularly cloned from human and other species. This transport is a mechanism to prevent overstimulation of receptors in the synapse.

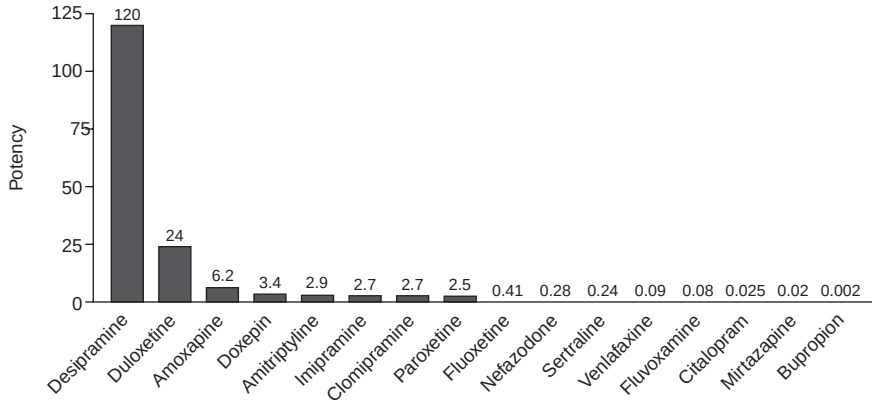
In general, antidepressants can block transport of the biogenic amine neurotransmitters norepinephrine, serotonin, and dopamine. They also can antagonize certain receptors, the most clinically relevant of which are presented here. In addition, some antidepressants inhibit the activity of monoamine oxidase, a ubiquitous enzyme that is important in the degradation of catecholamines (both norepinephrine and dopamine) and serotonin. Since this enzyme is present in mitochondria, which are found in nerve endings as well as in most other cells in the body, its

Table 1. Potency of Antidepressants for Blocking Some Neurotransmitter Transporters and Receptors[a]

	Neurotransmitter Transporters			Receptors		
Drug	NE	5-HT	DA	Histamine H_1	Muscarinic Acetylcholine	α_1-Adrenergic
Amitriptyline	+++	++++	–	+++++	+++	+++
Amoxapine	+++	+++	–	+++	+	+++
Bupropion	0	–	+	–	0	–
Citalopram	–	+++++	0	+	–	+
Clomipramine	+++	++++++	–	+++	+++	+++
Desipramine	+++++	+++	–	++	++	++
Doxepin	+++	+++	0	++++++	++	+++
Duloxetine	++++	++++++	+	–	–	–
Fluoxetine	++	+++++	–	–	–	–
Fluvoxamine	+	+++++	–	0	0	–
Imipramine	+++	+++++	–	++++	++	++
Mirtazapine	–	0	0	++++++	+	+
Nefazodone	++	++	++	+++	–	+++
Paroxetine	+++	++++++	+	0	++	–
Sertraline	+	++++++	+++	0	+	++
Venlafaxine	+	++++	–	0	0	0
Reference compounds						
Methylphenidate			+++			
Phentolamine						++++
Diphenhydramine				++++		
Atropine					+++++	

[a]Reprinted with permission from Richelson.[31]
Abbreviations: 5-HT = serotonin, DA = dopamine, NE = norepinephrine.
Symbols: + to ++++++ = increasing levels of potency, – = weak, 0 = no effect.

Figure 1. Inhibition by Antidepressants of the Human Norepinephrine Transporter[a]



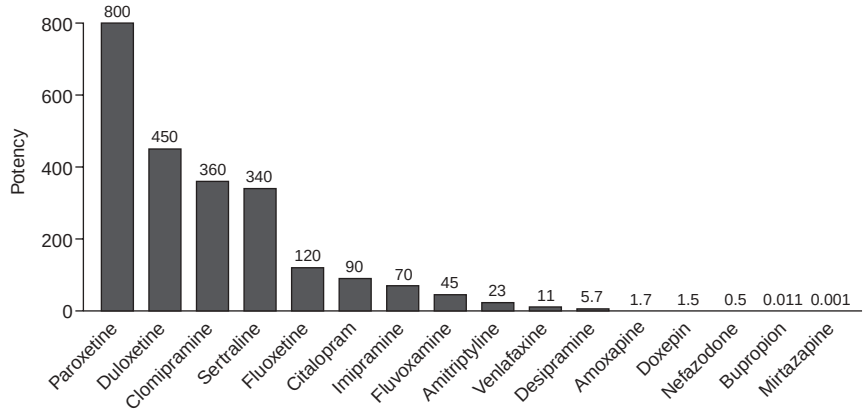
[a]The potency (affinity) data are expressed as the inverse of the equilibrium dissociation constant, K_d, multiplied by a factor of 10^{-7}. The K_d is in molarity. All data except those for duloxetine are from Tatsumi et al.[4] Data for duloxetine were derived from Richelson,[31] with the molecularly cloned human norepinephrine transporter by methods previously described.[4]

inhibition results in an elevation in the concentration of neurotransmitter available for release at the synapse.

SPECIFIC SYNAPTIC EFFECTS OF ANTIDEPRESSANTS AND THEIR POSSIBLE CLINICAL CONSEQUENCES

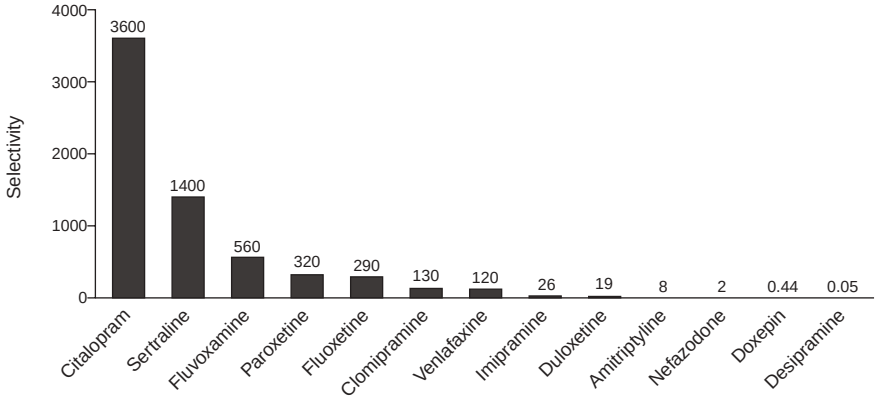
As previously alluded to and as presented elsewhere in this supplement, there are clinical data[1–3] to suggest that dual- or multi-action drugs, such as clomipramine, duloxetine, venlafaxine, and mirtazapine, have superior efficacy in treating depressed patients or have a more rapid onset of activity compared with single-action compounds. As will be seen in this section, clomipramine, duloxetine, and venlafaxine (at high dosages) block transport of both serotonin and norepinephrine. On the other hand, mirtazapine has no effects on transporters but has actions on some presynaptic receptors (α_2-adrenoceptors) that can increase the

Figure 2. Inhibition by Antidepressants of the Human Serotonin Transporter[a]



[a]The potency data are expressed as described in the legend to Figure 1. All data except those for duloxetine are from Tatsumi et al.[4] Data for duloxetine were derived from Richelson,[31] with the molecularly cloned human serotonin transporter by methods previously described.[4]

Figure 3. Selectivity of Antidepressants for Blocking Uptake of Serotonin Over Norepinephrine[a]



[a]Data are the ratios of the numbers presented in Figures 1 and 2.

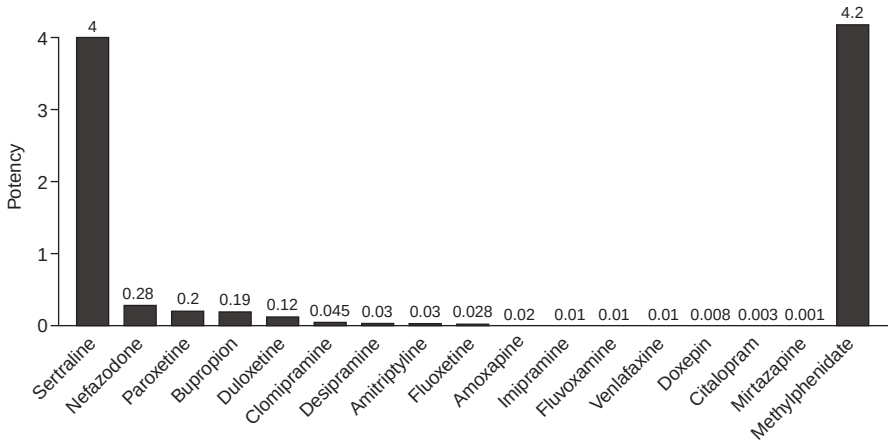
activity of serotonergic neurons and actions on some postsynaptic receptors (serotonin-2A [5-HT_{2A}]) that might be important for its therapeutic effects.

Blockade of Neurotransmitter Transport by Antidepressants

The vast majority of available antidepressants are neurotransmitter transport blockers (Table 1; Figures 1–4). In addition, most of these drugs, including older-generation compounds, are more potent at blocking transport of serotonin than transport of norepinephrine.[4] However, newer antidepressants are generally more selective and more potent than the older compounds at blocking transport of serotonin over norepinephrine. In addition, some antidepressants (e.g., mirtazapine) very weakly block transport of norepinephrine, serotonin, and dopamine. Bupropion is the only antidepressant more selective for blocking transport of dopamine than for other neurotransmitters. However, its effects on the dopamine transporter are relatively weak, and overall, bupropion may be more noradrenergic than dopaminergic due to the effects of a metabolite.[5]

Paroxetine is the most potent blocker of serotonin transport. Potency does not equate to selectivity, since citalopram, which is about 10-fold less potent than paroxetine, is by far the most selective blocker of serotonin transport (Figures 2 and 3). Selectivity is based on the ratio of 2 numbers: the drug's potency at serotonin transport blockade divided by its potency at norepinephrine transport blockade. It is more important to know the potency, rather than the selectivity ratio, to predict certain adverse effects and certain drug interactions. Finally, sertraline is the most potent of the antidepressants at blocking transport of dopa-

Figure 4. Antidepressant Inhibition of the Human Dopamine Transporter[a]



[a]The potency data are expressed as described in the legend to Figure 1. All data except those for duloxetine are from Tatsumi et al.[4] Data for duloxetine were derived from Richelson,[31] with the molecularly cloned human dopamine transporter by methods previously described. Methylphenidate is not an antidepressant, but it is shown here for comparison.[4]

mine (Figure 4), since it is about as potent as methylphenidate at this blockade.[4]

Venlafaxine has been called a serotonin-norepinephrine reuptake inhibitor (SNRI) on the basis of animal data.[7] However, as science progressed and the molecularly cloned human transporters were studied, it became clear that venlafaxine is much weaker at the human norepinephrine transporter than it is at the rat transporter. It is, therefore, an SSRI at low dosages (likely below 200 mg/day), with a selectivity for the human serotonin transporter over the human norepinephrine transporter of 120-fold (Figure 3). At high dosages (e.g., 375 mg/day), effects on the norepinephrine transporter can be achieved.[8] On the other hand, the new antidepressant duloxetine appears to be a potent blocker of both transporters, with a more balanced ratio of about 20 (Figures 1–3). Such data suggest that this compound will have effects on transporters for both serotonin and norepinephrine at the starting dosage.

Transporter blockade may be related to the mechanism of therapeutic effects of antidepressants. Additionally, blockade of both the noradrenergic and serotonergic transporters by an antidepressant may result in better rates of response.[1–3] Clinical data also suggest that serotonin transporter blockade is necessary for treatment of panic disorder and obsessive-compulsive disorder.[9–11]

Transport blockade of neurotransmitters likely relates to certain adverse effects of these antidepressant drugs and to some of their drug interactions (Table 2). For example, serotonin transport blockade is the property that causes sexual side effects, seen more commonly with the SSRIs than other types of antidepressants.[12] Serotonin promotes release of prolactin, while dopamine inhibits release of this hormone. Thus, elevation of prolactin levels can be seen with drugs that potently block the serotonin transporter.[13,14] Increased prolactin levels potentially can cause galactorrhea, menstrual changes, and sexual dysfunction in males (impotence).[15]

Serotonin transport blockade is also the property that causes serious results when a monoamine oxidase inhibitor is combined with an antidepressant (serotonergic syndrome).[16] In addition, researchers have reported adverse interactions between L-tryptophan, the precursor of serotonin, and fluoxetine,[17] as well as between St. John's wort *(Hypericum perforatum)*, which might have weak inhibitory effects on monoamine oxidase,[18] and antidepressants.[19]

Blockade of the dopamine transporter, as for the other transporters, may relate to antidepressant effects of drugs. It may be of benefit to patients with Parkinson's disease and mitigate against an increase in prolactin levels. It may also affect motivation and cognition. On the other hand, this property could cause psychomotor activation and precipitation or aggravation of psychosis, which has been seen very rarely with bupropion[20] and sertraline.[21]

Blockade of Neurotransmitter Receptors by Antidepressants

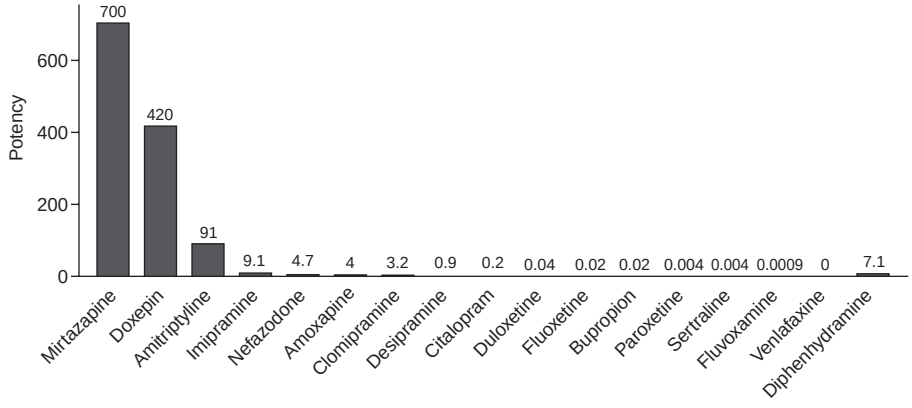
Although antidepressants interact with a multitude of neurotransmitter receptors (Table 1; Figures 5–7),[22–24] data for only 3 receptors of clinical relevance will be presented here. Most newer antidepressants are weaker than the older compounds (especially tricyclic antidepressants) at blocking receptors for neurotransmitters. This fact predicts a side effect profile for these newer compounds different from and more favorable than that for older drugs.

Table 2. Pharmacologic Properties of Antidepressants and Their Possible Clinical Consequences[a]

Property	Possible Clinical Consequences
Blockade of the norepinephrine transporter	Antidepressant effects Tremors Tachycardia Hypertension Blockade of the antihypertensive effects of guanethidine and guanadrel Augmentation of pressor effects of sympathomimetic amines
Blockade of the serotonin transporter	Antidepressant effects Antianxiety effects Anti-OCD effects Gastrointestinal disturbances (including weight loss early in treatment, weight gain late in treatment) Increase or decrease in anxiety (dose-dependent) Sexual dysfunction (including decreased libido) Extrapyramidal side effects Interactions with L-tryptophan, monoamine oxidase inhibitors
Blockade of the dopamine transporter	Antidepressant effects Enhanced motivation Enhanced cognition Mitigation against prolactin elevation Antiparkinsonian effect Psychomotor activation Aggravation of psychosis
Blockade of histamine H_1 receptors	Potentiation of central depressant drugs Sedation Drowsiness Weight gain
Blockade of muscarinic receptors	Antidepressant effects Blurred vision Attack or exacerbation of narrow angle glaucoma Dry mouth Sinus tachycardia Constipation Urinary retention Memory dysfunction
Blockade of α_1-adrenergic receptors	Potentiation of the antihypertensive effect of prazosin, terazosin, doxazosin, tamsulosin, and labetalol Postural hypotension, dizziness Reflex tachycardia

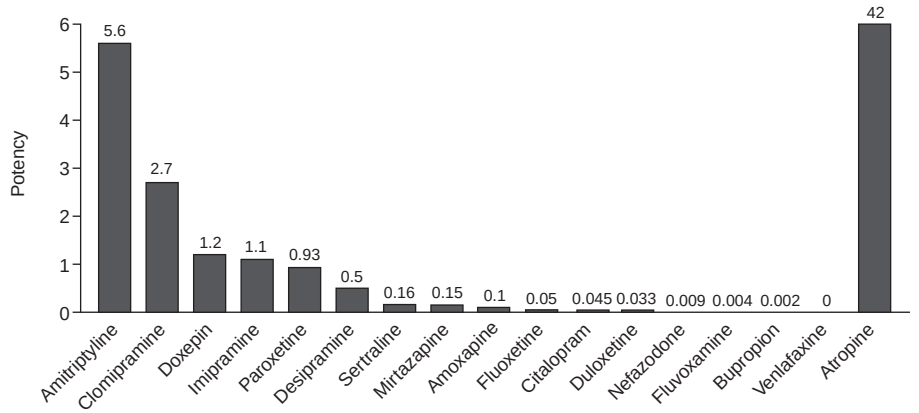
[a]Modified from Richelson.[6]
Abbreviation: OCD = obsessive-compulsive disorder.

Figure 5. Blockade by Antidepressants of Human Histamine H_1 Receptors[a]



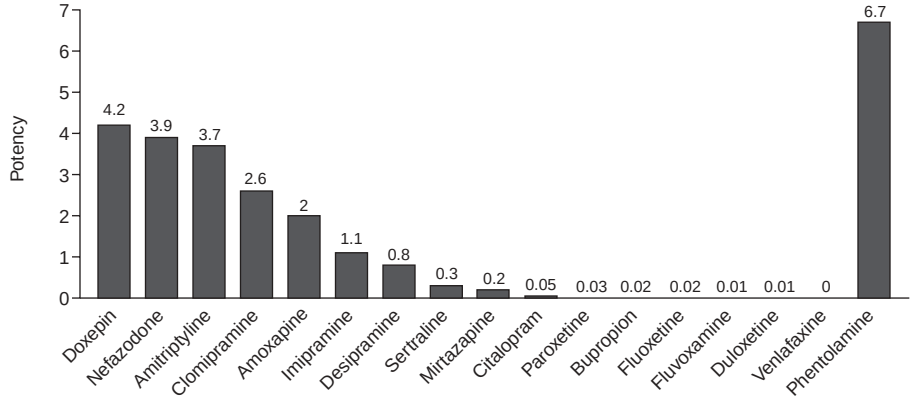
[a]The affinity data are expressed as described in the legend to Figure 1. All data except those for duloxetine were derived from radioligand binding studies with human brain tissue.[22,23] Data for duloxetine are from Wong et al.[24] and are based on IC_{50} (concentration at 50% inhibition of binding) at rat brain receptors. Diphenhydramine is not an antidepressant, but it is shown here for comparison.

Figure 6. Blockade by Antidepressants of Human Muscarinic Receptors[a]



[a]The affinity data are expressed as described in the legend to Figure 1. All data except those for duloxetine were derived from radioligand binding studies with human brain tissue.[22,23] Data for duloxetine are from Wong et al.[24] Atropine is not an antidepressant, but it is shown here for comparison.

Figure 7. Blockade by Antidepressants of Human α_1-Adrenoceptors[a]



[a]The affinity data are expressed as described in the legend to Figure 1. All data except those for duloxetine were derived from radioligand binding studies with human brain tissue.[22,23] Data for duloxetine are from Wong et al.[24] Phentolamine is not an antidepressant, but it is shown here for comparison.

Of all the receptor interactions of antidepressants, in general the most potent effect is at histamine H_1 receptors. In fact, some antidepressants are such exceedingly potent histamine H_1 antagonists (Figure 5) that they are more potent than all of the newer-generation histamine H_1 antagonists marketed in recent years in the United States. As a result, clinicians are using them to treat allergic and dermatologic problems.[25]

A drug interaction of antidepressants related to histamine H_1 receptor antagonism is the potentiation of the effects of central depressant drugs, which cause sedation and drowsiness. This antagonism is probably responsible for these side effects. Sedation, however, may be a desired effect in patients who are agitated and also depressed. This property also may be responsible for weight gain, as has been strongly correlated for weight gain with antipsychotic drugs.[26]

For antidepressants, the next most potent receptor blocking effect that is of certain clinical relevance is at the muscarinic acetylcholine receptor. Antidepressants have a broad range of affinities for human brain muscarinic receptors (Figure 6). The most potent is amitriptyline. The SSRI paroxetine is unique among the newer compounds for having appreciable antimuscarinic potency, similar to that for imipramine (Figure 6). However, it is not likely that at the usual dosage of paroxetine (20 mg/day) there will be significant effect on muscarinic receptors. Nonetheless, if the dosage is increased or the usual dosage is

given to a slow metabolizer, anticholinergic side effects may be seen.[27]

Although blockade of muscarinic receptors may be related to therapeutic effects,[28] more likely this receptor blockade by some antidepressants is responsible for several adverse effects (Table 2). Thus, vigilance is especially necessary with elderly patients to avoid or reduce the antimuscarinic effects of antidepressants.

At the α_1-adrenoceptor, the most potent compounds, although a little weaker than the antihypertensive drug phentolamine, are likely to have effects clinically at these receptors (Figure 7). This receptor blockade by antidepressants may be responsible for orthostatic hypotension, a most serious and common cardiovascular effect of these drugs.[29] This side effect can cause dizziness and a reflex tachycardia. In addition, this property of antidepressants will result in the potentiation of several antihypertensive drugs that potently block α_1-adrenoceptors (Table 2).

DISCUSSION

Blockade of transporters and receptors by antidepressants occurs shortly after a patient has ingested a dose of medication. Thus, most of the possible adverse effects discussed occur early in the treatment of patients. However, with chronic administration of the drug, adaptive changes may occur that can result in an adjustment to certain side effects, the development of new side effects, and the onset of therapeutic effects. The reader should keep in mind that, as a first approximation, the drugs that are most potent at the properties discussed are more likely to cause these possible clinical effects than the drugs that are weak at these properties. What is meant by "first approximation" is that there are many more variables to consider, in addition to affinity for a transporter or a receptor, in predicting the likelihood that a drug will cause an adverse effect. The true prediction is based on knowledge of certain variables that at this time cannot be readily measured. More specifically, it is the concentration of the drug at the site of action, relative to its affinity (or more correctly, the inverse of the affinity, which is the concentration of drug at 50% of its maximal binding) for this site that determines how much of the drug will be bound to its target.[30] However, this is the case only in the absence of neurotransmitter competing for binding to the same site and in the absence of biological variability of the target (i.e., structural differences affecting binding affinity).[30] Assuming no biological variability, one needs to know the concentration not only of the drug, but also of the neurotransmitter at the target. Presently, it is possible to obtain this information in only a very limited way, with positron emission tomography scanning.

Nonetheless, clinically, these synaptic effects can be linked to therapeutic and certain adverse effects. Knowledge of these effects helps elucidate the advantages of newer compounds relative to the older compounds, and differences among new compounds in terms of their side effect profiles and certain drug interactions. Specifically, new antidepressants with selective effects on blocking both serotonin and noradrenergic transporters (e.g., duloxetine and high-dose venlafaxine) may provide therapeutic advantages over single-action compounds. Thus, the in vitro findings presented should help clinicians choose the most appropriate antidepressant for each patient and, potentially, will help to maximize efficacy and prevent or minimize the occurrence of certain adverse effects and drug interactions.

Drug names: amitriptyline (Endep, Elavil, and others), atropine (Atropen and others), bupropion (Wellbutrin and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), diphenhydramine (Ambenyl, Benadryl, and others), doxazosin (Cardura and others), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), labetalol (Trandate, Normodyne, and others), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phentolamine (Regitine and others), prazosin (Minizide, Minipress, and others), sertraline (Zoloft), tamsulosin (Flomax), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, duloxetine has not been approved by the U.S. Food and Drug Administration for treatment of major depressive disorder.

REFERENCES

1. Vestergaard P, Gram LF, Kragh-Sorensen P, et al. Therapeutic potentials of recently introduced antidepressants. Danish University Antidepressant Group. Psychopharmacol Ser 1993;10:190–198
2. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000;58:19–36
3. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
4. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340:249–258
5. 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
6. Richelson E. Pharmacology of antidepressants—characteristics of the ideal drug. Mayo Clin Proc 1994;69:1069–1081
7. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci 1993;52:1023–1029
8. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. Arch Gen Psychiatry 2000;57:503–509
9. Evans L, Kenardy J, Schneider P, et al. Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks—a double-blind comparison of zimeldine, imipramine and placebo. Acta Psychiatr Scand 1986;73:49–53
10. Murphy DL, Zohar J, Benkelfat C, et al. Obsessive-compulsive disorder as a 5-HT subsystem-related behavioural disorder. Br J Psychiatry 1989; 155:15–24
11. Nutt DJ, Forshall S, Bell C, et al. Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. Eur Neuropsychopharmacol 1999;9(suppl 3):S81–S86
12. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85
13. Amsterdam JD, Garcia-Espana F, Goodman D, et al. Breast enlargement during chronic antidepressant therapy. J Affect Disord 1997;46:151–156
14. Egberts ACG, Meyboom RHB, DeKoning FHP, et al. Non-puerperal

lactation associated with antidepressant drug use. Br J Clin Pharmacol 1997;44:277–281
15. Buvat J, Lemaire A, Buvat-Herbaut M, et al. Hyperprolactinemia and sexual function in men. Horm Res 1985;22:196–203
16. Gillman PK. Serotonin syndrome: history and risk. Fundam Clin Pharmacol 1998;12:482–491
17. Steiner W, Fontaine R. Toxic reaction following the combined administration of fluoxetine and L-tryptophan: five case reports. Biol Psychiatry 1986;21:1067–1071
18. Deltito J, Beyer D. The scientific, quasi-scientific and popular literature on the use of St John's wort in the treatment of depression. J Affect Disord 1998;51:345–351
19. Lantz MS, Buchalter E, Giambanco V. St John's wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatry Neurol 1999;12:7–10
20. Golden RN, James SP, Sherer MA, et al. Psychoses associated with bupropion treatment. Am J Psychiatry 1985;142:1459–1462
21. Popli AP, Fuller MA, Jaskiw GE. Sertraline and psychotic symptoms: a case series. Ann Clin Psychiatry 1997;9:15–17
22. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984;230:94–102
23. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology 1994;114:559–565
24. Wong DT, Bymaster FP, Mayle DA, et al. LY248686, a new inhibitor of serotonin and norepinephrine uptake. Neuropsychopharmacology 1993;8: 23–33
25. Drake LA, Fallon JD, Sober A, et al. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. J Am Acad Dermatol 1994;31:613–616
26. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
27. Boyer WF, Blumhardt CL. The safety profile of paroxetine. J Clin Psychiatry 1992;53:61–66
28. Janowsky DS, Overstreet DH, Nurnberger JI. Is cholinergic sensitivity a genetic marker for the affective disorders? Am J Med Genet 1994;54: 335–344
29. Glassman AH. Cardiovascular effects of antidepressant drugs: updated. Int Clin Psychopharmacol 1998;13(suppl 5):S25–S30
30. Preskorn SH. A message from Titanic. J Pract Psychiatry Behav Health 1998;4:236–242
31. Richelson E. The clinical relevance of antidepressant interaction with neurotransmitter transporters and receptors. Psychopharmacol Bull 2002; 36:133–149