

Norepinephrine Involvement in Antidepressant Action

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Because of the introduction and popularity of the selective serotonin reuptake inhibitor (SSRI) antidepressants, much attention was centered on the indolealkylamine 5-hydroxytryptamine, or serotonin. To some extent, this focus on serotonin occurred at the expense of the catecholamine neurotransmitter norepinephrine. Nevertheless, it has been apparent for almost 40 years that selective blockers of norepinephrine reuptake may be antidepressants (e.g., desipramine). This brief review covers the acute pharmacologic effects that may be responsible for the efficacy of currently marketed antidepressants as well as that of reboxetine, a newly developed selective norepinephrine reuptake inhibitor. Also discussed is the fact that the acute pharmacologic profile of selective reuptake inhibitors often predicts effects they produce when given long term. For example, the long-term administration of SSRIs produces certain effects on serotonergic systems, but not noradrenergic ones. By contrast, selective norepinephrine reuptake inhibitors, when given long term, modify certain noradrenergic parameters, but not serotonergic indices. Finally, it is speculated how drugs that enhance central noradrenergic transmission might ameliorate the symptoms of depression. *(J Clin Psychiatry 2000;61[suppl 10]:25-30)*

Twenty-one drugs are currently approved for the treatment of major depression in the United States. They have been grouped in various ways. The original antidepressants—tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)—have been referred to as typical or first-generation antidepressants, with all subsequent drugs being termed atypical or second-generation antidepressants. Such a classification results in the latter group's being quite heterogeneous. Perhaps a more useful classification would be to group them based on their presumed mechanism of action (Table 1). If one does this, 4 categories of antidepressants result. First, there are drugs that selectively block the uptake of norepinephrine (NE). The potency of many antidepressants to cause this effect is shown in Figure 1.¹⁻⁵ Such drugs include the TCAs desipramine, nortriptyline, and protriptyline as well as the newer

TCA-like compounds maprotiline and amoxapine (Figure 2). A new selective norepinephrine reuptake inhibitor, reboxetine, is likely to be marketed soon in the United States. As shown in Figure 3, its structure is distinct from that of the TCAs or TCA-like drugs.

Second, there are drugs that selectively block the reuptake of 5-hydroxytryptamine (5-HT), or serotonin. Figure 4 presents the potency of antidepressants at blocking the reuptake of 5-HT. Such selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, fluvoxamine, sertraline, citalopram, and paroxetine.

A third group of drugs act nonselectively on noradrenergic and serotonin neurons. Examples of drugs that fall into this category include the nonselective TCA uptake inhibitors amitriptyline and imipramine. Although these drugs are slightly more potent in vitro at inhibiting the uptake of NE than that of 5-HT (Figure 5), they do not show any selectivity in vivo.⁶ Also included in this group are MAOIs such as phenelzine and tranylcypromine.

Two unusual examples of drugs fall into this category. Venlafaxine can block the uptake of both 5-HT and NE. Although it is slightly more potent in vitro in blocking the uptake of 5-HT than that of NE (see Figure 5), its selectivity ratio of 4- to 6-fold is usually not considered sufficiently large to confer selectivity in vivo. Nevertheless, in many patients, at the lower doses used clinically (e.g., 75 mg daily), venlafaxine appears to act primarily as an SSRI. At higher doses (and it is difficult presently to state with certainty if this is 150 or 225 mg daily or even higher), it blocks the uptake of NE as well as that of 5-HT. Thus, venlafaxine appears to be the only antidepressant currently marketed whose pharmacologic profile as an uptake inhibitor changes as the dose is raised.

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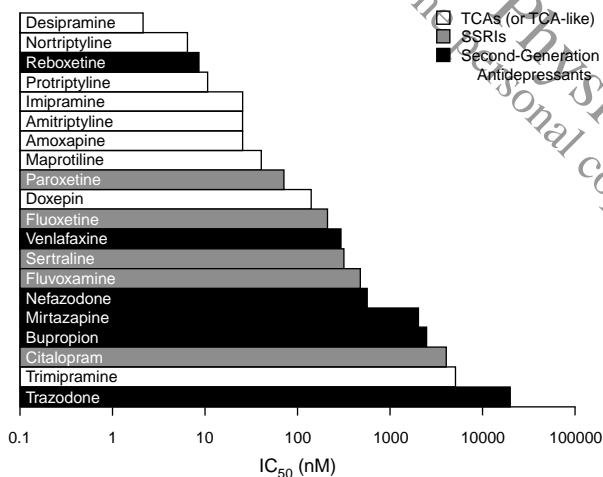
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Table 1. Proposed Classification for Antidepressants Based on Presumed Mechanisms of Action^a

Proposed Classification	Drug Name	Current Classification (if any)
Selective blockade of NE reuptake (selective norepinephrine reuptake inhibitors)	Desipramine, nortriptyline, protriptyline	TCAs
	Amoxapine, maprotiline	TCA-like
	Reboxetine	Class by itself
Selective blockade of 5-HT reuptake (SSRIs)	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	SSRIs
Nonselective action on NE and 5-HT neurons	Amitriptyline, imipramine	TCAs
	Phenelzine, tranylcypromine	MAOIs
Unknown potent stimulatory effects on NE or 5-HT	Trimipramine	TCA
	Bupropion	Class by itself
	Nefazodone	Class by itself
	Trazodone	Class by itself

^aAbbreviations: 5-HT = serotonin, MAOI = monoamine oxidase inhibitor, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

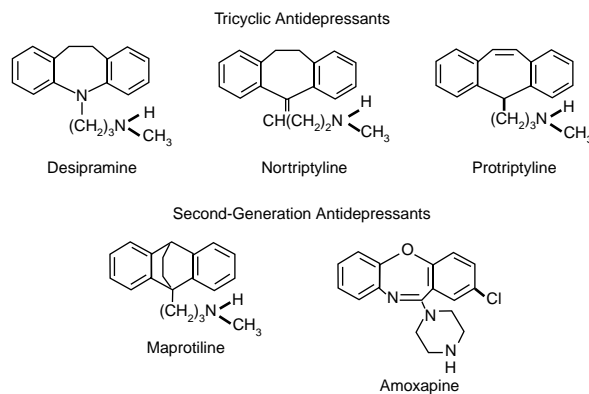
Figure 1. Potency of Antidepressants to Block the Uptake of Norepinephrine (NE)^a



^aData from references 1–5. Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Some values have been adjusted to reflect not only the absolute potencies of the drugs in blocking the uptake of NE but also their relative potencies in relationship to each other. The more potent the drug, the lower the IC₅₀ value.

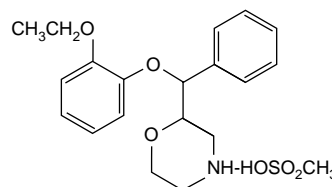
The second somewhat unusual drug that seems to act through both noradrenergic and serotonergic mechanisms is mirtazapine. It does not appear to be a potent inhibitor of the uptake of either NE or 5-HT (see Figures 1 and 4). Rather, mirtazapine appears to be an antagonist of the noradrenergic autoreceptors that reside on the soma and dendrites as well as terminals of noradrenergic neurons.¹ These autoreceptors, which are of the α_2 subtype, cause inhibition of the release of NE from noradrenergic nerves. By blocking such autoreceptors, mirtazapine removes this inhibitory influence on noradrenergic transmission. This

Figure 2. Structures of Drugs That Selectively Block the Reuptake of Norepinephrine^a



^aNote that the tricyclic antidepressants have a 3-ring (tricyclic) molecular core and the second-generation compounds also have a 3 joined-ring structure.

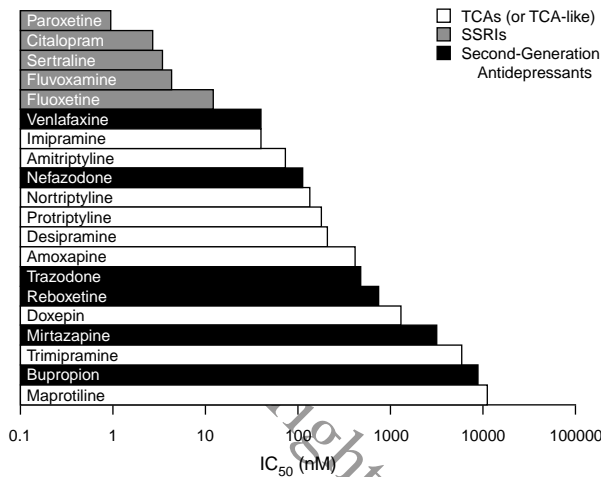
Figure 3. The Structure of Reboxetine, (2RS, α RS)-2-[α -2-(ethoxyphenoxy)benzyl] Morpholine Methanesulphonate^a



^aNote that its chemical structure is distinct from that of the other selective norepinephrine reuptake inhibitors shown in Figure 2.

facilitates neurotransmission that is mediated by NE. Thus, by a different mechanism from reuptake inhibition, mirtazapine directly enhances noradrenergic transmission. However, mirtazapine indirectly enhances serotonergic transmission as well.⁷ This enhancement is due to a facilitatory noradrenergic input onto serotonergic soma and dendrites located in the raphe nuclei. The activation by NE of the α_1 -adrenoceptors that are located on the serotonergic soma increases the firing rate of these neurons and enhances the release of 5-HT.⁸ Thus, the α_2 antagonist property of mirtazapine directly facilitates noradrenergic transmission and, as such, enhances neurotransmission in raphe nuclei and produces an increased release of 5-HT from serotonergic terminals.

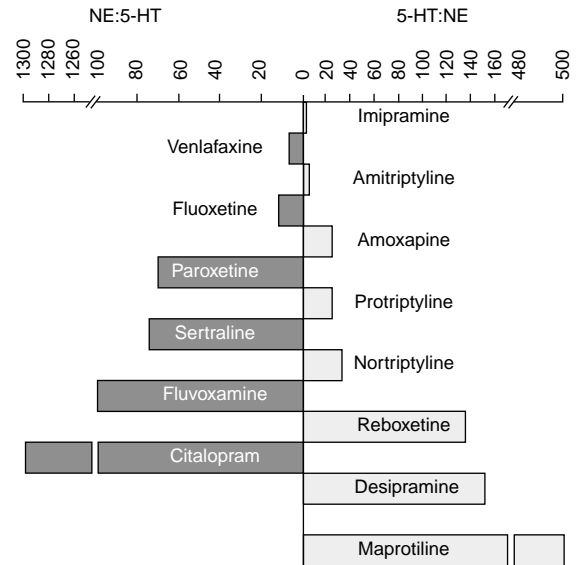
Fourth, and last in the mechanism of action classification scheme, would be a heterogeneous group of drugs that do not have known potent effects that would cause stimulation of either NE- or 5-HT-containing neurons. In other words, we really do not understand how these drugs produce their antidepressant effects. An early example of a drug in this category is the TCA trimipramine. This drug is a very weak inhibitor of the reuptake of either NE or 5-HT (see Figures 1 and 4) and is not an MAOI. Bupropion

Figure 4. Potency of Antidepressants to Block the Uptake of Serotonin^a

^aData from references 1–5. Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Some values have been adjusted to reflect not only the absolute potencies of the drugs in blocking the uptake of serotonin but also their relative potencies in relationship to each other. The more potent the drug, the lower the IC₅₀ value.

may also fall in this category (see Figures 1 and 4). It is often stated that bupropion may act through dopaminergic mechanisms since it is the only antidepressant that more potently blocks the reuptake of dopamine than that of either NE or 5-HT.⁹ However, it deserves emphasis that bupropion is a relatively weak inhibitor in vitro of the uptake of dopamine. Perhaps this is why data are conflicting as to whether it produces inhibition of dopamine reuptake at clinically relevant doses.¹⁰ Some have reported effects on noradrenergic function in bupropion-treated patients.¹¹ However, the uptake of ³H-NE into rat cortical tissue was not inhibited to any substantial degree (8%–31%) when the assays were carried out in plasma from patients treated with bupropion.¹² This reviewer therefore concludes that the mechanism of action of bupropion as an antidepressant remains unknown.

Two other drugs in this last category are nefazodone and trazodone. These drugs are very weak inhibitors of the reuptake of NE and are relatively weak at inhibiting the reuptake of 5-HT as well (see Figures 1 and 4). Administration of reasonable doses of nefazodone to healthy volunteers produced much less inhibition of 5-HT reuptake into platelets than that caused by SSRIs.¹³ In view of this, it is unlikely that trazodone will inhibit 5-HT reuptake in patients since nefazodone is about 5 times more potent than trazodone in inhibiting the reuptake of 5-HT (see Figure 4). Actually, the most potent pharmacologic property of these 2 drugs on serotonergic parameters is their antagonism of 5-HT_{2A} receptors.¹⁴ If enhancement of serotonergic transmission is one mechanism of antidepressant effi-

Figure 5. Ratios of IC₅₀ Values for Uptake Inhibition^a

^aAbbreviations 5-HT = serotonin, NE = norepinephrine. Bars extending to the right represent drugs more potent at inhibiting the uptake of NE than that of 5-HT. Bars extending to the left show drugs more potent at inhibiting the uptake of 5-HT than that of NE. Potency is inversely related to the IC₅₀ values. To achieve a selectivity ratio greater than 1, the IC₅₀ value for the monoamine transporter at which the drug is most potent is made the denominator of the ratio.

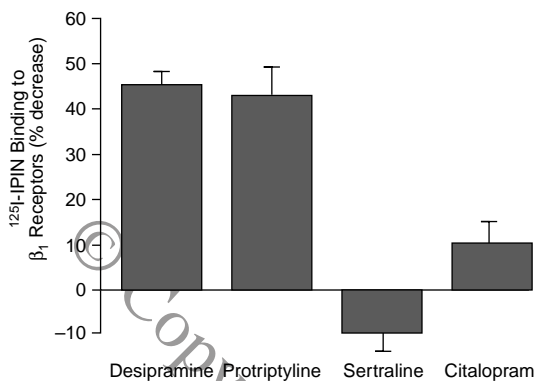
ciacy, it is unclear how antagonism of the 5-HT_{2A} receptor would cause such enhancement. In conclusion, acute pharmacologic properties that contribute to the efficacy of drugs such as trimipramine, bupropion, nefazodone, and trazodone remain unknown.

LONGER-TERM PHARMACOLOGIC EFFECTS

The pharmacologic effects that have just been discussed are primary, direct effects of the drug (e.g., inhibition of uptake, monoamine oxidase, or autoreceptors). They can be measured in vitro as well as in vivo and occur very shortly after drug administration. However, it is well established that it takes weeks, perhaps as many as 12, for maximal therapeutic effects of antidepressants to occur. Further, some believe that it takes 2 to 3 weeks for real drug effects to become evident,^{15–17} although this view has been challenged.^{18,19} Such a time dependency for clinical efficacy led to a de-emphasis in research on the acute pharmacologic effects of antidepressants. Rather, attention has been focused on the more slowly developing or chronic effects of antidepressants on central monoamine systems. The purpose of this article is not to review such effects in detail; the interested reader can find such information elsewhere.²⁰

The relevant issue discussed here is whether drugs that have acute selective effects maintain such selectivity upon

Figure 6. Effect of Antidepressants on Down-Regulation of β_1 -Adrenoceptors in the Basolateral Nucleus of the Amygdala^a

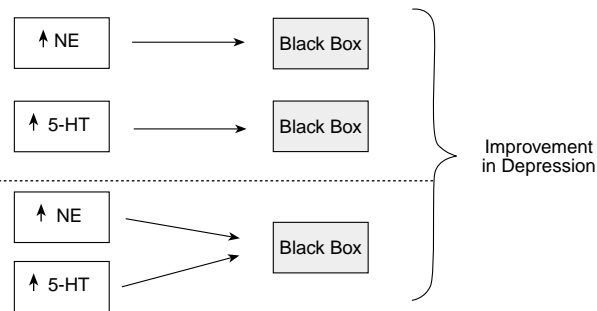


^aData from Ordway and colleagues.²⁸ Abbreviations: MAOI = monoamine oxidase inhibitor, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor. The binding of ¹²⁵I-iodopindolol (¹²⁵I-IPIN) to β -adrenoceptors was measured by quantitative autoradiography. ICI 118,551, a selective β_2 -adrenoceptor antagonist, was used to block the binding of ¹²⁵I-IPIN to β_2 -adrenoceptors. Repeated administration to rats of drugs that block the uptake of NE, such as desipramine and protriptyline, as well as MAOIs, significantly reduced the binding of ¹²⁵I-IPIN. By contrast, repeated administration of SSRIs did not.

repeated administration. In other words, would an SSRI, for example, produce effects on noradrenergic parameters upon repeated administration, or would its long-term effects still be confined to serotonergic function? A similar question can be asked about selective noradrenergic drugs. In vitro selectivity might be lost upon repeated drug administration in vivo (reviewed in Frazer²¹). For example, evidence exists of anatomical interactions between noradrenergic and serotonergic neurons. As mentioned previously, there is noradrenergic innervation of serotonergic cell body areas. There is also serotonergic innervation of the locus ceruleus, an area of brain containing many noradrenergic cell bodies.²² Although evidence suggests direct activation of serotonergic cell firing by NE acting on α_1 receptors,⁸ how 5-HT modifies noradrenergic cell firing is less clear. Other types of interactions between the 2 biogenic amine systems are possible. For example, the release of 5-HT from serotonergic terminals may be tonically inhibited by NE acting on α_2 -adrenergic heteroreceptors on serotonergic nerves.²³

Despite these findings, much of the data generated on the long-term effects of selective drugs on monoamine systems over time reveal that selective acute effects lead to selective longer-term effects. That is to say, repeated administration of drugs that acutely block NE reuptake selectivity causes adaptive effects in noradrenergic, but not serotonergic, systems. For example, a well-established, long-term effect of certain antidepressants is the production of β -adrenoceptor subsensitivity accompanied by the down-regulation (decrease in density) of such receptors.²⁴⁻²⁷ We have found this effect to be produced in rat brain, par-

Figure 7. Speculative Models for Antidepressant Efficacy^a



^aAbbreviations: 5-HT = serotonin, NE = norepinephrine. The model at the top of the figure indicates separate, noninteracting pathways for behavioral improvement caused by drugs that act selectively on noradrenergic or serotonergic nerves. Both preclinical and clinical data do not show that it is necessary, for example, for a noradrenergic drug to influence serotonergic function in order for it to be effective. However, the model shown at the bottom of the figure, in which activation of either noradrenergic or serotonergic neurotransmission produces a similar effect on some intermediary process, cannot be ruled out.

ticularly in certain amygdaloid nuclei, by repeated administration of drugs such as desipramine, protriptyline, phenelzine, and tranylcypromine. These drugs acutely affect noradrenergic function. By contrast, SSRIs, which acutely have no effect on noradrenergic function, do not produce β -adrenoceptor down-regulation upon repeated administration (Figure 6).²⁸

On the other hand, we have found specific effects on serotonergic parameters caused by repeated administration of SSRIs that are not reproduced by similar administration of antidepressants that are weak inhibitors of 5-HT reuptake. For example, hypothermia is elicited in rats by systemic administration of agonists at 5-HT_{1A} receptors. In rats treated repeatedly with SSRIs such as sertraline or citalopram (or with MAOIs), subsensitive hypothermic responses were elicited by activation of 5-HT_{1A} receptors. Such subsensitive responses were not seen in rats treated repeatedly with desipramine or trazodone.²⁹ More recently, we found that repeated administration of SSRIs to rats caused a down-regulation of the serotonin transporter throughout the brain. Again, desipramine did not produce this effect.³⁰

Perhaps the best data available on selective agents ameliorating depressive symptomatology through specific effects on monoamine systems are the clinical studies from the research groups associated with Dennis Charney and Pedro Delgado.^{31,32} In an elegant series of studies, these investigators found that inhibiting serotonin synthesis caused a recurrence of symptomatology in depressed patients who had been treated successfully with an SSRI and were being maintained with such drugs. In contrast, inhibition of serotonin synthesis did not cause a return of symptoms in patients who were treated successfully with desipramine or nortriptyline.³¹ Thus, selective inhibitors of NE reuptake

seem less dependent on the availability of 5-HT for their beneficial effects than SSRIs do. By contrast, selective inhibitors of NE reuptake are dependent on the availability of catecholamines for their beneficial clinical effects, whereas SSRIs are not.³² Such data not only emphasize that selective agents seem to produce their efficacy through different monoamine systems, but also that these monoamine neurotransmitters are involved in the mechanisms of action of these drugs.

Taken together, it may be inferred from such data that drugs with selective effects on noradrenergic or serotonergic neurons produce their beneficial effects either (1) through separate or distinct mechanisms or (2) by affecting some common downstream modality (Figure 7). One such speculative downstream function, for example, might be antagonism of corticotropin-releasing factor function.³³ The top mechanism in Figure 7 might imply additive effects of noradrenergic and serotonergic drugs, whereas the one on the bottom suggests the effects of these 2 types of drugs, when combined, would be potentiated. At present, there is little conclusive evidence favoring one or the other mechanism shown in Figure 7. That different types of antidepressants seem to have equivalent efficacy in nonselected depressed patients, i.e., drugs that directly affect both NE and 5-HT neurons (amitriptyline), are no more efficacious than desipramine or SSRIs does not help one to know which mechanism is correct. To determine this, one would need to use doses of drugs that do not produce maximal (or optimal) clinical efficacy, and, of course, this is not how clinical trials are carried out.

BEHAVIORAL EFFECTS OF NORADRENERGIC ACTIVATION

A final issue to be addressed is how enhancement of central noradrenergic function might lead to the amelioration of depressive symptomatology. We do not precisely know the answer to this question. It is known that noradrenergic neurons originating from cell bodies in the brainstem such as those in the locus ceruleus ascend to many brain regions thought to be involved in some of the symptoms associated with depression and/or in regulating responses to stimuli (stressors) that might precipitate or exaggerate depressive symptomatology.³⁴ For example, it has long been known that the locus ceruleus is activated by various stressors (see Jacobs and colleagues³⁵) with the resultant release of NE helping to coordinate the appropriate response to the stressor.³⁶ "Stress" has been implicated as a causative factor in the development of depression, at least in some individuals. Perhaps drug-induced activation of central noradrenergic neurons facilitates the depression-prone individual to respond more appropriately to environmental stressors.

Perhaps the strongest case for a behavioral role for NE can be made for its involvement in behavioral arousal (or

alerting or vigilance³⁷; see Aston-Jones et al.³⁸). In particular, it is of interest that only stimuli considered of significance to the organism activate the locus ceruleus so as to initiate attentional and emotional processes. Again, although speculative, involvement of NE in such processes results, perhaps, in drug-induced activation of central noradrenergic pathways' being helpful in overcoming the limited emotionality, flat affect, and, perhaps, even anhedonia that is associated with depression.

Other behaviors in which NE has been implicated, either specifically or because of its role in behavioral arousal, include learning (or subprocesses that contribute to it, such as attention) and cognition, the cycling of sleep and wakefulness, and perhaps feeding behavior.^{36,39,40} Again, these behaviors are known to be altered in patients with depression. It may well be that the activation of central noradrenergic neurons is useful in restoring normal behavioral functioning.

There is an additional and/or alternative way to consider drug-induced activation of noradrenergic neurons in the amelioration of depressive symptomatology. As previously mentioned, tonic activation of noradrenergic nerves establishes a general behavioral state that could influence the specific behaviors described above. In addition, phasic activation of noradrenergic nerves at the cellular level increases the signal-to-noise ratio of evoked activity in circuits innervated by noradrenergic neurons.^{41,42} At the behavioral level, this cellular effect translates into facilitation of specific sensory/motor responses to environmental stimuli.^{43,44} Such phasic enhancement of responsivity might also be helpful to the patient experiencing fatigue or loss of energy, cognitive impairment, loss of libido, or anhedonia. It will be necessary to integrate what is known about the cellular and behavioral effects of NE with the known pharmacologic effects of antidepressants and the behavioral manifestations of the syndrome of depression if we are to truly further our understanding of drug efficacy in depression.

SUMMARY AND CONCLUSIONS

Many different approaches to the modification of neurotransmitter concentrations in the synapses of important brain regions appear to result in effective antidepressants. In other words, drugs that cause selective activation of either noradrenergic or serotonergic neurotransmission can be antidepressants, as can drugs that nonselectively activate these neuronal systems. Interestingly, a number of antidepressants, both old and new, do not have potent pharmacologic effects that would cause enhancement of transmission mediated by either 5-HT or NE. It is not clear how such drugs (e.g., trimipramine, bupropion, nefazodone) produce their beneficial effects.

Antidepressant-induced activation of central noradrenergic transmission might produce behavioral improvement

in several ways. Tonic activation of noradrenergic nerves establishes a behavioral state involving arousal that may aid in restoring appropriate cognitive, motoric, feeding, and sleep-wake behaviors in the depressed patient. Phasic activation of noradrenergic transmission facilitates sensory/motor responses to environmental stimuli, which could result in additional behavioral improvements in the depressed patient.

Drug names: amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), citalopram (Celexa), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), protriptyline (Vivactil), reboxetine (Vestra), sertraline (Zoloft), transylpromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil), venlafaxine (Effexor).

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