Pharmacology of Antidepressants: Selectivity or Multiplicity?

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The understanding of mechanisms of antidepressant action has evolved over time. The strong antidepressant activity of the tricyclic antidepressants (TCAs) has supported the role of both norepinephrine and serotonin (5-HT) in depression and the mechanism involved in antidepressant action. The next generation of antidepressants included the selective serotonin reuptake inhibitors (SSRIs), further supporting the role of serotonin, while the selective norepinephrine reuptake inhibitors such as maprotiline and reboxetine underlined the relevance of norepinephrine. These developments suggest that either facilitation of serotonin or norepinephrine or both may lead to an antidepressant response. The next step was the development of mixed serotonin-norepinephrine reuptake inhibitors (SNRIs), exemplified by venlafaxine and milnacipran. As with the TCAs, the antidepressant activity of SNRIs is based on inhibition of norepinephrine and serotonin reuptake, but unlike TCAs they do not have anticholinergic, antihistaminergic, and cardiotoxic effects. Although norepinephrine is known to stimulate serotonin cell firing rate via the α_1-adrenoceptors, norepinephrine and serotonin have independent antidepressant actions. The latest development has been the introduction of the noradrenergic and specific serotonergic antidepressant mirtazapine. Its antidepressant effect appears to be related to dual enhancement of central noradrenergic and serotonergic neurotransmission by blockade of α_2-adrenoceptors. In addition, mirtazapine directly blocks 5-HT_2 and 5-HT_3 receptors, which may account for its anxiolytic and sleep-improving properties as well as its lack of adverse events that are typical of SSRIs. *(J Clin Psychiatry 1999;60[suppl 17]:4–8)*

The understanding of mechanisms of antidepressant action has evolved over time. In the 1960s, tricyclic antidepressants (TCAs) were found to act by inhibiting the reuptake of monoamines, especially serotonin (5-HT) and norepinephrine. However, TCAs also have other multiple pharmacologic properties that are held responsible for most of their side effects. The discovery that specific effects on monoamine uptake are important for antidepressant action led to the development of new antidepressants designed to be pharmacologically more selective. These new drugs included the selective serotonin reuptake inhibitors (SSRIs) and, more recently, a selective norepinephrine reuptake inhibitor (NRI). In general, these drugs have fewer serious side effects and are therefore better tolerated than the TCAs and monoamine oxidase inhibitors (MAOIs).

Recent studies, however, have challenged the notion that antidepressant selectivity is always better than multiple action. The latest antidepressants, including noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and milnacipran, derive their therapeutic benefits from simultaneous action on both monoamine systems. In addition, by blocking specific serotonin receptors, antidepressants such as mirtazapine also reduce the undesired effects associated with SSRIs and SNRIs.

MODE OF ACTION

Antidepressants can be classified into 3 groups according to their principal mode of action: reuptake inhibitors, which inhibit monoamine uptake at the synaptic cleft; monoamine oxidase inhibitors, which inhibit monoamine degradation (e.g., moclobemide); and α_2-adrenoceptor antagonists, which act at specific receptors to affect the monoamine system. Mirtazapine blocks the α_2-adrenergic receptors, leading to an effect on both noradrenergic and serotonergic systems in the brain.[1] Reuptake inhibitors can be further divided into 3 categories: SSRIs, which are selective for serotonin (e.g., paroxetine); selective NRIs, which are selective for norepinephrine (e.g., reboxetine, TCAs); and SNRIs, which inhibit the uptake of serotonin and norepinephrine (e.g., venlafaxine, TCAs).

Reuptake inhibitors are categorized based on their relative potency to block the serotonin and norepinephrine uptake site. SSRIs are more potent at the serotonin reuptake

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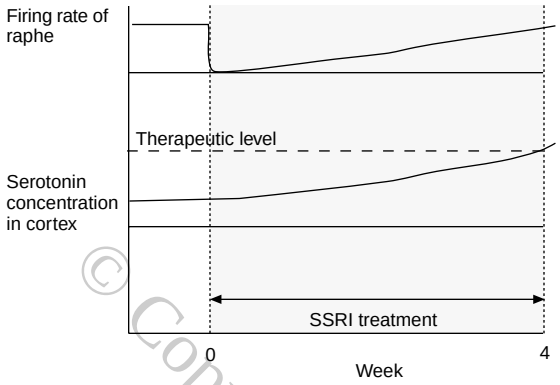
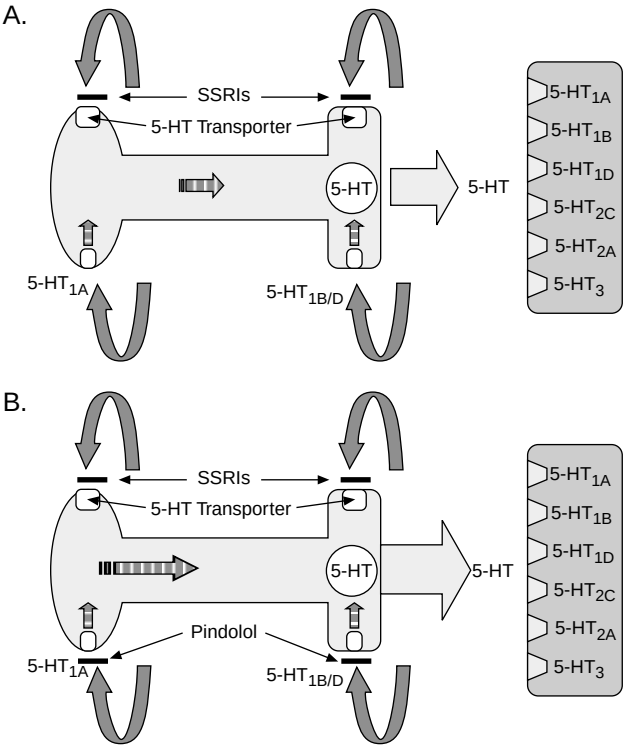
Figure 1. Time Lag of SSRIs[a]



[a]Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

Figure 2. The Serotonergic Synapse[a]



[a]Increased serotonin in the cell body and terminal region, which is the product of SSRI activity, (A) activates 5-HT_{1A} and 5-HT_{1B} receptors, resulting in decreased serotonin release in the terminal region and a decreased firing rate in the cell body region and thus reduced clinical response. The addition of drugs such as pindolol (B) that block 5-HT_{1A} and 5-HT_{1B} receptors can hasten clinical response to SSRIs.

site, while selective NRIs more or less selectively inhibit norepinephrine uptake. SNRIs inhibit the reuptake of both monoamines to roughly the same extent. TCAs are generally classed as SNRIs or selective NRIs, but clomipramine is considered to be an SSRI, although its major metabolite is effective as a selective NRI. In addition to their effects on uptake mechanisms, TCAs have multiple other pharmacologic properties and thus are nonselective agents, whereas reboxetine and venlafaxine are both selective agents.

ONSET OF RESPONSE

Although blockade of reuptake occurs almost immediately upon administration of an SSRI, the clinical effect of reuptake inhibitors is delayed for 3 to 4 weeks (Figure 1). Microdialysis and electrophysiologic studies in animals have revealed that this delay in efficacy parallels the change in neuronal activity of the monoamine neurons. Reuptake inhibitors increase the release of serotonin and/or norepinephrine, but at the same time decrease neuronal activity (firing rate), which partly abolishes the effect on the release of serotonin or norepinephrine. However, with continued treatment, neuronal activity is restored, resulting in a gradual increase in serotonin release, which parallels clinical efficacy.

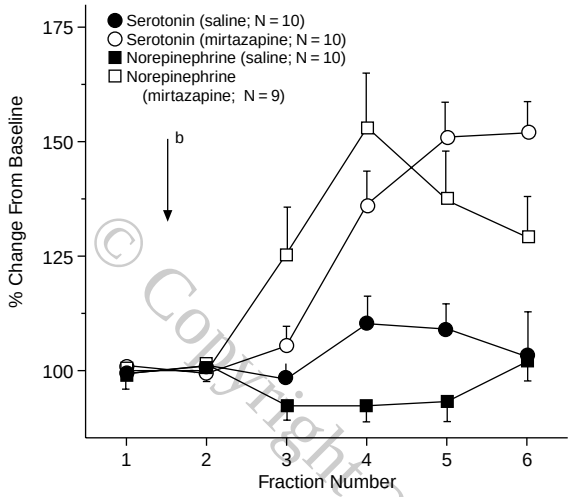
Figure 2 illustrates in detail the mechanisms operating in the serotonin system. Presynaptic 5-HT_1 autoreceptors play an important role in the regulation of both the release of neurotransmitter and neuronal activity of the neurons. Increased levels of serotonin in the cell body region activate the 5-HT_{1A} receptors. As a consequence, neuronal firing is decreased, resulting in a decrease of serotonin release. Activation of the 5-HT_{1B} receptors in terminal areas also attenuates the terminal release. These secondary effects of reuptake inhibitors nullify or at least substantially reduce the effect of these agents on serotonin release and reduce the immediate clinical response. With long-term treatment, these inhibitory receptors become less sensitive, resulting in a gradual attenuation of the restraining effects and an increase of serotonin release in the brain. This increase parallels clinical efficacy.

If this explanation of the delay in onset of efficacy with reuptake inhibitors is correct, one would expect drugs that block these receptors to hasten the clinical response. Pindolol can block both 5-HT_{1A} and 5-HT_{1B} receptors. In animals, pretreatment with this drug significantly stimulates serotonin release in the cortex, but clinical data are as of yet equivocal. However, some investigators have reported a hastening and augmentation of the effect of SSRIs.[2] These data do suggest that drugs capable of blocking neurotransmitter release by controlling receptors may have clinically relevant effects.

MIRTAZAPINE

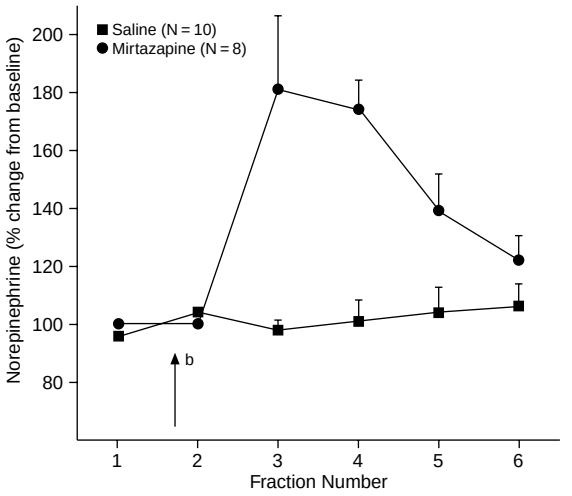
Mirtazapine is a new antidepressant with a novel mechanism of action. It has been shown to block norepinephrine release by controlling α_2-autoreceptors in the brain. In

Figure 3. Effect of Mirtazapine on Serotonin and Norepinephrine Release in the Hippocampus[a]



[a]Data from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).
[b]Point of administration.

Figure 4. Effect of Mirtazapine on Norepinephrine Release in the Locus Ceruleus[a]



[a]Data from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).
[b]Point of administration.

Table 1. Summary of Affinity of Antidepressants for Various Receptors[a]

Antidepressants	α_2-Adrenoceptors (K_d)	α_1-Adrenoceptors (K_d)	5-HT_{2A} Receptors (K_d)
Mirtazapine	100	400	10
Mianserin	73	34	7
Venlafaxine	> 10,000	> 10,000	> 10,000
SSRIs	> 4000	> 3000[b]	> 4000[c]
TCAs	> 3000[d]	20–90	20–120

[a]Data from references 4–7. K_d is the equilibrium dissociation constant, in nM. Abbreviation: 5-HT = serotonin, TCAs = tricyclic antidepressants.
[b]N.B. sertraline = 380.
[c]N.B. fluoxetine = 210.
[d]N.B. amitriptyline = 690.

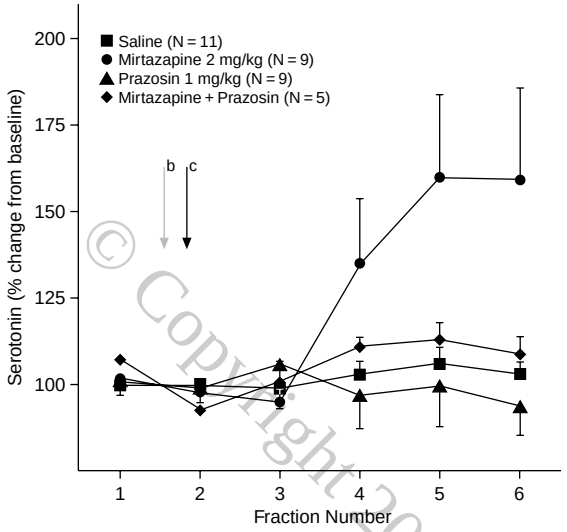
vivo microdialysis studies have shown that mirtazapine has a dual mode of action that increases both norepinephrine and serotonin levels in the brain. Although attained by different mechanisms, the effect of mirtazapine on monoamine release resembles that of the SNRIs at high doses. In addition, mirtazapine also blocks 5-HT_2 and 5-HT_3 receptors, activation of which is held responsible for many of the undesired effects of SSRIs and SNRIs. Figure 3 illustrates the effect of mirtazapine on both serotonin and norepinephrine release in rat hippocampus in vivo.[3] Upon administration of mirtazapine, both norepinephrine and serotonin levels are elevated to almost the same extent, demonstrating mirtazapine's dual effect.

Mirtazapine is unique in that it has a clinically relevant affinity for the α_2-adrenoceptor (Table 1).[4–7] Mianserin is virtually the only other antidepressant to have this property, although mianserin also binds to the α_1-adrenoceptor.[8] Mirtazapine has no appreciable effect on the α_1-adrenoceptor, whereas it has an affinity for 5-HT_{2A} receptor similar to that of mianserin and other TCAs. Mirtazapine is the only antidepressant capable of blocking the 5-HT_3 receptor.

Mirtazapine's main action is the blockade of the α_2-adrenoceptors, which should enhance the release of norepinephrine in the brain since these receptors control the firing rate (in cell body region) and the release (in the terminal region) of norepinephrine. Because the effect results from the blockade of the release-inhibitory receptors, one would not expect this effect to be delayed. A measurement of the release of norepinephrine in the locus ceruleus, the principal cell body region of the noradrenergic system, was used to assess the effect of mirtazapine on the neuronal firing rate, since increased neuronal activity is reflected by an increase in norepinephrine release in that region (Figure 4).[3] The data show that acute administration of mirtazapine significantly elevates the neuronal activity of the noradrenergic system, resulting in an increase in the norepinephrine release in the cortex.

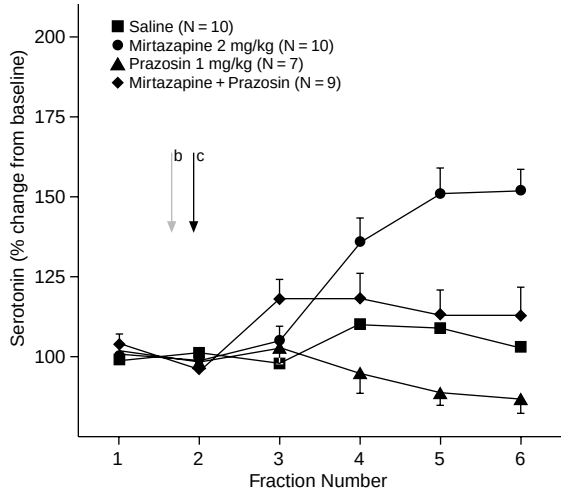
To fully understand the effect of mirtazapine on the serotonergic system, we must take into account the neuronal cross talk between the 2 monoamine systems. Firstly, noradrenergic fibers impinge on serotonergic cell bodies in the raphe region. Norepinephrine released in the serotonergic cell body region stimulates the serotonergic firing through α_1-adrenoceptors located on these cell bodies. Since mirtazapine leaves this receptor unaffected, it is expected to stimulate the serotonin firing rate and as a consequence, serotonin release in the brain. Secondly, norepinephrine, which is released in the hippocampus and other brain regions, inhibits serotonin release through α_2-heteroreceptors

Figure 5. Effect of Mirtazapine and Prazosin on Serotonin Release in the Median Raphe Nucleus[a]



[a]Data from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).
[b]Point of administration for prazosin or saline.
[c]Point of administration for mirtazapine or saline.

Figure 6. Effect of Mirtazapine and Prazosin on Serotonin Release in the Hippocampus[a]



[a]Data from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).
[b]Point of administration for prazosin or saline.
[c]Point of administration for mirtazapine or saline.

located on serotonin neuron terminals. Mirtazapine also blocks α_2-heteroreceptors at this neuronal site, reinforcing the effect on the firing rate and subsequent serotonin release in those areas where this interaction is present.

To further investigate the importance of α_1 receptor stimulation on mirtazapine's mechanism of serotonin release, the effect of the addition of prazosin was studied. Prazosin is an antihypertensive agent that is a selective α_1-adrenoceptor blocker. As seen in Figure 5, mirtazapine significantly enhanced serotonin neuronal activity.[3] Prazosin itself had virtually no effect on serotonin activity, but was able to block the effect of mirtazapine almost completely. The effect of mirtazapine and prazosin addition on serotonin release in the hippocampus is shown in Figure 6.[3] Mirtazapine increases the serotonin release, primarily through stimulation of α_1-adrenoceptors, located on serotonin cell bodies, and addition of prazosin attenuates this effect.

Table 2. Side Effects Associated With the Stimulation of Different Neurotransmitter Systems[a]

5-HT (overall)
Nausea
Migraine
Gastrointestinal problems
Sexual dysfunction
Norepinephrine
Tachycardia
Tremors
Potentiation of sympathomimetics
5-HT receptors
5-HT_1
Hypophagia
5-HT_2
Jitteriness
Nervousness
Insomnia
Sexual dysfunction
5-HT_3
Nausea
Vomiting
Other neurotransmitter systems
Histamine H_1
Sedation
Weight gain
Muscarinic
Dry mouth
Blurred vision
Confusion (elderly)
Constipation
Tachycardia
Urinary retention
α_1-Adrenergic
Postural hypotension
Reflex tachycardia
Potentiation of antihypertensives
Drowsiness
Dizziness

[a]Based on references 4 and 9.

Side Effects

Stimulation of the serotonergic and noradrenergic systems plays a crucial role in the mechanism of action of antidepressants; however, one may also expect some associated side effects. Some of the frequently observed side effects related to the stimulation of various neurotransmitter systems in the brain are shown in Table 2.[4,9] The affinities of various antidepressants to these neurotransmitter systems are shown in Table 3. TCAs have high affinity for

Table 3. Affinity of Antidepressants for the Histamine H_1, Muscarinic, and α_1-Adrenergic Receptors[a]

Antidepressant(s)	Histamine H_1	Muscarinic	α_1-Adrenergic
Mirtazapine	++	–	–
Mianserin	++	–	++
Venlafaxine	–	–	–
SSRIs	–	–	–
TCAs	+	++	+

[a]Symbols: ++ = high, + = moderate, – = low.

histamine H_1, muscarinic, and α_1-adrenergic receptors, leading to a wide range of undesirable side effects. However, selectivity of pharmacologic action on a single neurotransmitter system does not necessarily equate to fewer side effects. Given the global effect of serotonin on brain function and the large number of receptors involved, one may expect an array of side effects. In particular, stimulation of 5-HT_2 and 5-HT_3 receptors is associated with some of the undesired effects of the SSRIs and the SNRIs, such as nausea and insomnia. Blocking these receptors may lessen these side effects, lending strength to the theory that specific multiplicity of action could have an advantage over selective action. In addition to its global effect on serotonin release, mirtazapine also blocks the 5-HT_2 and 5-HT_3 receptors and therefore is associated with fewer adverse effects related to the stimulation of these receptors. In addition, it is free of muscarinic and α_1-adrenergic side effects.[10]

CONCLUSIONS

In conclusion, mirtazapine is a new dual-acting antidepressant with a novel mechanism of action. It enhances noradrenergic and serotonergic neurotransmission but blocks 5-HT_2 and 5-HT_3 receptors. Like the SNRIs, it enhances the availability of both norepinephrine and serotonin, but has a different mechanism of action that should preclude any delay in the onset of clinical efficacy. In contrast to the SSRIs and the SNRIs, its effect on the serotonin system is specific by virtue of its 5-HT_2 and 5-HT_3 blocking properties, resulting in better tolerability.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil and others), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), pindolol (Visken), prazosin (Minipress and others), sertraline (Zoloft), venlafaxine (Effexor).

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