

# Pharmacology of Rapid-Onset Antidepressant Treatment Strategies

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Although selective serotonin reuptake inhibitors (SSRIs) block serotonin (5-HT) reuptake rapidly, their therapeutic action is delayed. The increase in synaptic 5-HT activates feedback mechanisms mediated by 5-HT<sub>1A</sub> (cell body) and 5-HT<sub>1B</sub> (terminal) autoreceptors, which, respectively, reduce the firing in 5-HT neurons and decrease the amount of 5-HT released per action potential resulting in attenuated 5-HT neurotransmission. Long-term treatment desensitizes the inhibitory 5-HT<sub>1</sub> autoreceptors, and 5-HT neurotransmission is enhanced. The time course of these events is similar to the delay of clinical action. The addition of pindolol, which blocks 5-HT<sub>1A</sub> receptors, to SSRI treatment decouples the feedback inhibition of 5-HT neuron firing and accelerates and enhances the antidepressant response. The neuronal circuitry of the 5-HT and norepinephrine (NE) systems and their connections to forebrain areas believed to be involved in depression has been dissected. The firing of 5-HT neurons in the raphe nuclei is driven, at least partly, by  $\alpha_1$ -adrenoceptor-mediated excitatory inputs from NE neurons. Inhibitory  $\alpha_2$ -adrenoceptors on the NE neuroterminals form part of a feedback control mechanism. Mirtazapine, an antagonist at  $\alpha_2$ -adrenoceptors, does not enhance 5-HT neurotransmission directly but disinhibits the NE activation of 5-HT neurons and thereby increases 5-HT neurotransmission by a mechanism that does not require a time-dependent desensitization of receptors. These neurobiological phenomena may underlie the apparently faster onset of action of mirtazapine compared with the SSRIs.

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The delay in onset of action remains one of the most perplexing and undesirable characteristics of antidepressant drugs. During the latent period, patients remain exposed to the serious morbidity and mortality risks of their illness. Moreover, the adverse effects of antidepressants are frequently at their worst during the early phase of treatment, and compliance can be significantly impaired by the combination of lack of efficacy and adverse effects.

The delay in the onset of significant symptom relief is typically 2 to 4 weeks and is consistent across all types of antidepressant drug therapy. However, this does not imply that the therapeutic response is endowed with an inertia that is impossible to overcome. Indeed, a single night of sleep deprivation, for example, produces an antidepressant re-

sponse, albeit temporary, in 60% to 80% of patients.<sup>1</sup> Electroconvulsive therapy commonly produces a response after 2 or 3 treatments during the first week.<sup>2,3</sup> Reduction of plasma tryptophan, which induces a consequent reduction in serotonin (5-HT) synthesis, by dietary manipulation causes prompt relapse of depression in patients who have responded to antidepressant drugs. Interestingly, this effect is greater in patients who had responded to selective serotonin reuptake inhibitors (SSRIs) than in those who had responded to the norepinephrine (NE) reuptake inhibitor desipramine, thus implying a specific 5-HT effect for SSRIs.<sup>4</sup> The relapses are equally promptly reversed after administration of tryptophan. In contrast, desipramine-responsive patients relapsed on administration of a catecholamine synthesis inhibitor, which lowers dopamine, NE, and epinephrine, indicating that the primary noradrenergic action of desipramine may be contributing extensively to the antidepressant response attained with this agent.

Taken together, these data show that, although the therapeutic response to antidepressant drugs is delayed, the antidepressant response per se is not endowed with an intractable inertia. Thus, if sleep deprivation, electroconvulsive therapy, and dietary tryptophan manipulation can evoke rapid therapeutic responses, it should be possible, in principle at least, to design drug therapies without delayed onset of action.

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**Table 1. Placebo-Controlled Studies of the Use of Pindolol to Accelerate the Therapeutic Effect of Antidepressants<sup>a</sup>**

Study	N	Accelerated Onset	Greater Efficacy
Maes et al, 1996 <sup>7</sup>	33	-	+
Perez et al, 1997 <sup>8</sup>	111	+	+
Tome et al, 1997 <sup>9</sup>	80	+	-
Bordet et al, 1998 <sup>10</sup>	101	+	-
Zanardi et al, 1997 <sup>11</sup>	63	+	+
Zanardi et al, 1998 <sup>12</sup>	72	+	-
Berman et al, 1999 <sup>13</sup>	86	-	-

<sup>a</sup>Symbols: + = positive finding, - = negative finding. All studies used selective serotonin reuptake inhibitors (SSRIs). An accelerated onset of antidepressant action was either a significantly shorter period before achieving a 50% reduction in symptom severity or a significant difference between the placebo group and the pindolol group during the first month. Greater efficacy was defined as a greater proportion of responders or remitters after 4 to 6 weeks of pindolol/SSRI treatment when compared with the placebo/SSRI group, or as a greater decrease in symptom severity.

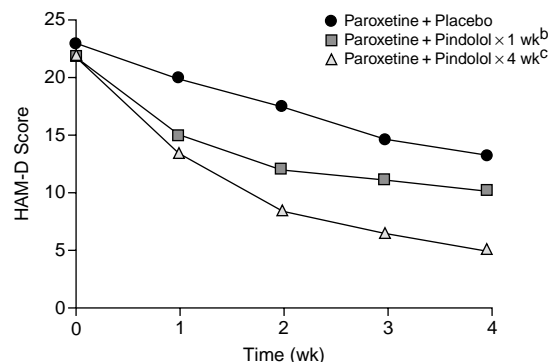
### MECHANISM OF ACTION OF SSRIs

The mechanism for the delayed onset of action of antidepressants is now becoming clear; it has been known for many years that enhancement of neurotransmission in 5-HT and/or NE neurons underlies the mechanism of action of antidepressant drugs. However, although antidepressants have properties that apparently potentiate monoamine neurotransmission acutely, their net effect is more complex. The SSRIs, for example, are specific blockers of 5-HT reuptake (i.e., they do not block dopamine or NE reuptake to a significant extent), and, although they have other, less potent, pharmacologic actions, this is the only property that this structurally diverse group of compounds have in common. It is reasonable, therefore, to suppose that they act via the 5-HT system. However, although the SSRIs reach the brain within minutes or hours after administration, and effects on 5-HT uptake can be measured almost immediately, their therapeutic effect is delayed for 2 to 4 weeks.

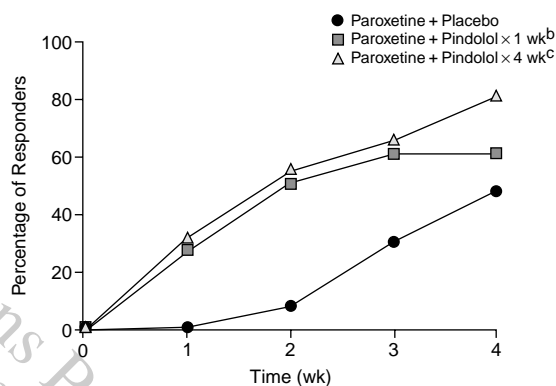
The first action of an SSRI after acute administration is blockade of 5-HT reuptake in both terminal areas and cell body. Reuptake blockade in the cell body region causes overactivation of inhibitory 5-HT<sub>1A</sub> autoreceptors that reduce the generation of action potentials and thereby reduce 5-HT release in postsynaptic terminal areas. Thus, despite the blockade of 5-HT reuptake, 5-HT release in terminal projection areas of 5-HT neurons is reduced, not enhanced, by acute administration of SSRIs. However, with continued SSRI treatment and exposure to elevated 5-HT concentrations in the cell body areas, these 5-HT<sub>1A</sub> autoreceptors become desensitized and the firing of 5-HT neurons is normalized. The terminal 5-HT<sub>1B</sub> autoreceptors, which control the amount of 5-HT released per electrical impulse, also become desensitized after 2 to 3 weeks of SSRI administration. This desensitization occurs in the presence of re-

**Figure 1. Effect of Pindolol on Delay in Onset of the Antidepressant Effect of Paroxetine<sup>a</sup>**

#### A. Changes in Severity of Depression



#### B. Survival Curves of Time to Response



<sup>a</sup>Adapted, with permission, from Zanardi et al.<sup>11</sup>

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

<sup>b</sup>Pindolol received for 1 week of paroxetine treatment; placebo received for remaining 3 weeks.

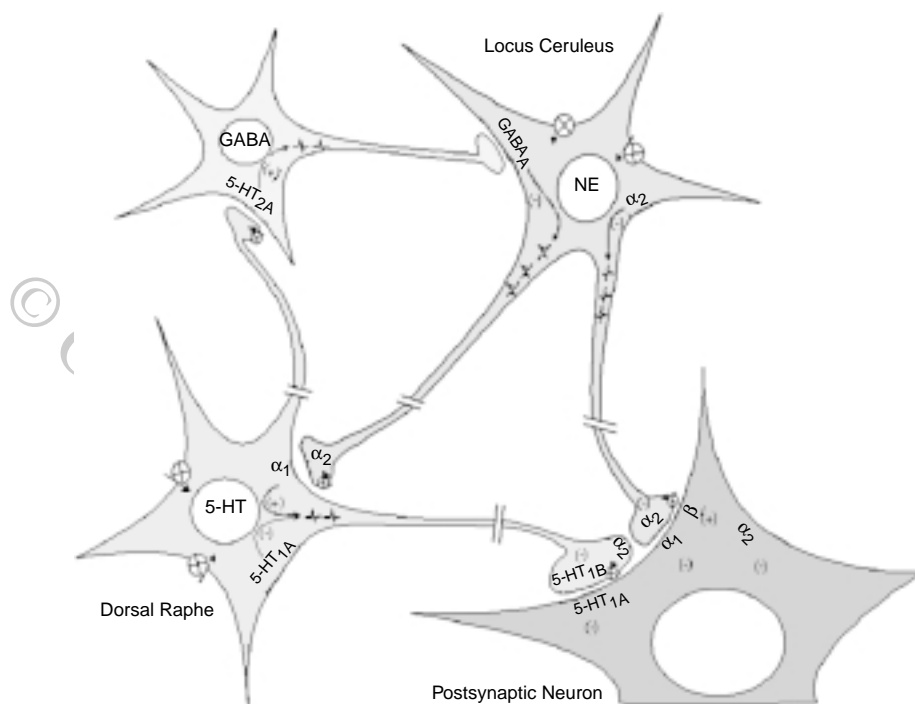
<sup>c</sup>Pindolol received for all 4 weeks of paroxetine treatment.

uptake blockade in terminal areas, so that 5-HT neurotransmission is enhanced. Most interestingly, these neurobiological changes occur along a time course similar to that for the onset of action of antidepressant activity.<sup>5</sup>

### ACCELERATION OF CLINICAL RESPONSE WITH PINDOLOL

If, as these findings suggest, 5-HT<sub>1A</sub> autoreceptor desensitization plays a significant role in the biological substrate of the delay in the onset of action of antidepressants, an opportunity is afforded for pharmacologic interventions to bypass this step and therefore accelerate the onset of action of antidepressants. Administering a preferential antagonist of 5-HT<sub>1A</sub> autoreceptors would avoid the overstimulation of the 5-HT<sub>1A</sub> autoreceptors and perhaps accelerate the antidepressant response. The agent that has been

Figure 2. Interaction Between Serotonin (5-HT) and Norepinephrine (NE) Neurons and Their Projections to Pyramidal Cells of the Hippocampus<sup>a</sup>



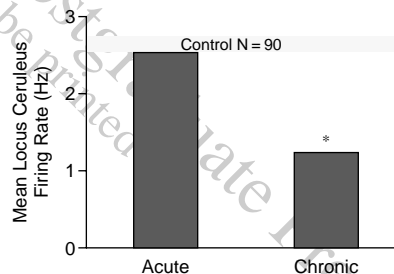
<sup>a</sup>Abbreviations: 5-HT = serotonin, GABA =  $\gamma$ -aminobutyric acid, NE = norepinephrine.

best investigated to date is pindolol, which, as well as being a  $\beta$ -adrenoceptor antagonist, also has a structure similar to 5-HT and is a potent 5-HT<sub>1A</sub> antagonist.<sup>6</sup> To date, 6 of 8 double-blind, placebo-controlled trials have shown that pindolol can accelerate the onset of antidepressant effect of SSRIs (Table 1). Typical results (from the 1997 study by Zanardi et al.<sup>11</sup>) are shown in Figure 1, which illustrates the degree of acceleration of antidepressant action that is produced, at least in some patients. After 2 weeks of paroxetine alone, very few patients (around 10%) had achieved response, whereas in the paroxetine + pindolol groups, around 60% of patients were in response. In the studies shown in Table 1, the mean reduction in the latency of onset of action of the SSRIs was in the range of 5 to 14 days.

### INTERACTIONS BETWEEN 5-HT AND NE

The foregoing discussion has only considered the 5-HT system; however, it is clear that the NE system also has an important role to play in the etiology of depression and the mechanism of action of antidepressants. Electrophysiologic and pharmacologic studies have delineated in detail the interactions between the 5-HT and NE neurons and their projections to the forebrain (Figure 2).<sup>14</sup> 5-HT

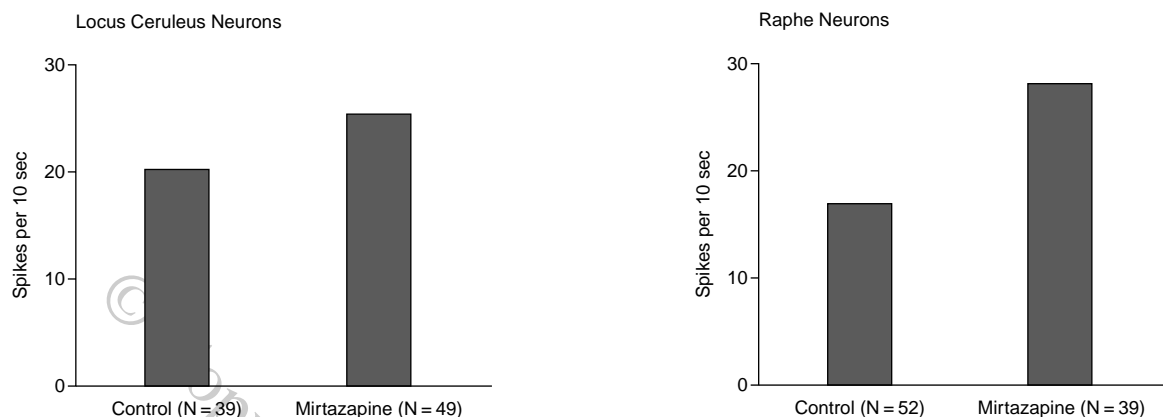
Figure 3. Effect on Acute (2-day) and Chronic (21-day) Administration of Paroxetine (10 mg/kg/day) on the Firing Rate of Locus Ceruleus Norepinephrine Neurons in Rats<sup>a</sup>



<sup>a</sup>Reprinted, with permission, from Szabo and colleagues.<sup>15</sup> The horizontal shaded area represents the range of control observations. \*p < .05, Tukey test.

neurons project to NE cell bodies that are located in the locus ceruleus, where they have an inhibitory effect via a presynaptic 5-HT<sub>1A</sub>-receptor and a postsynaptic 5-HT<sub>2</sub> receptor. It is possible that the overactivation of the inhibitory 5-HT projection to the NE cell bodies may be counterproductive as far as the antidepressant efficacy of SSRIs is concerned. This is possible for 2 reasons: firstly, NE transmission is involved in the mechanism of action of antide-

Figure 4. Effect of Chronic Administration of Mirtazapine (5 mg/kg/day) on Norepinephrine and Serotonin Neuron Firing in the Locus Ceruleus and Raphe of Rats<sup>a</sup>



<sup>a</sup>Reprinted, with permission, from Haddjeri and colleagues.<sup>22</sup>

pressants in its own right, and secondly, the NE system is an important tonic driver of raphe neurons, so inhibition of locus ceruleus neurons will also, indirectly, inhibit 5-HT neurotransmission (see Figure 2).

As shown in Figure 3, chronic, but not acute, administration of an SSRI inhibits firing in (and thus release of NE from) locus ceruleus neurons.<sup>15</sup> The time course of this effect is similar to that of the desensitization of 5-HT<sub>1A</sub> receptors previously discussed.<sup>14</sup>

### MIRTAZAPINE: ONSET OF ACTION AND MECHANISM OF ACTION

Although the results from specifically designed prospective onset-of-action studies with mirtazapine are awaited, there is good circumstantial evidence from post hoc analyses that mirtazapine has a faster onset of therapeutic action than SSRIs. Several statistical methodologies are available to evaluate onset of action (reference 16 and S. A. Montgomery, M.D.; P. Bech, M.D.; et al., manuscript submitted, 2001), and these have been applied to the clinical database of mirtazapine. The results of meta-analyses of responder/remission rates,<sup>17</sup> pattern analysis,<sup>18</sup> and survival analytical approaches<sup>19</sup> have consistently indicated that mirtazapine has a faster onset of action than the SSRIs.

Mirtazapine is not an inhibitor of 5-HT reuptake, so where does its mechanism of action fit in the neurobiology of monoaminergic neurons? It potently blocks the  $\alpha_2$ -adrenoceptor on the cell bodies on NE and 5-HT nerve terminals in the forebrain, but also blocks the inhibitory  $\alpha_2$ -adrenoceptor on 5-HT terminals in the locus ceruleus and on NE terminals in the raphe nuclei as well as throughout the brain.<sup>20,21</sup> These effects of mirtazapine on 5-HT

Table 2. Neurobiological Effects of Long-Term Antidepressant Treatment<sup>a</sup>

Treatment	5-HT		NE		Overall Effect on 5-HT Transmission
	Firing	Reuptake Inhibition	Firing	Reuptake Inhibition	
Mirtazapine	+	0	+	0	++
SSRIs	0	++	-	0	+
Venlafaxine	0	++	-	+	++

<sup>a</sup>Abbreviations: 5-HT = serotonin, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor. Symbols: 0 = no effect; + or - = changes in firing, significant reuptake inhibition, or enhanced transmission; ++ = a potent effect. The overall effect on transmission is arrived at by the algebraic summation of the individual effects of the drugs on firing and reuptake.

and NE neurocircuitry have been dissected and verified. Firstly, mirtazapine increases locus ceruleus firing by itself and attenuates the inhibition of these neurons by the  $\alpha_2$ -adrenoceptor antagonist clonidine. Conversely, a clonidine-induced decrease in locus ceruleus firing is reversed by mirtazapine. Moreover, not only does mirtazapine increase firing in NE neurons, but it also increases NE release by blocking the  $\alpha_2$ -adrenoceptor on NE nerve terminals. Mirtazapine will consequently increase NE release throughout the brain. However, NE neurons also project to the raphe nuclei, where they exert an excitatory effect on 5-HT neurons via an  $\alpha_1$ -adrenoceptor. The fact that prazosin, an  $\alpha_1$ -adrenoceptor antagonist, suppresses raphe firing suggests not only that the excitatory  $\alpha_1$ -adrenoceptors exist on 5-HT neuronal cell bodies, but that there is a tonic NE-mediated excitation of 5-HT neurons.<sup>20</sup> The effect of mirtazapine is to further increase raphe firing. In these studies,<sup>20,21</sup> mirtazapine was administered acutely via the intravenous route, but similar results are obtained following extended administration using osmotic mini-pumps (Figure 4).<sup>22,23</sup>

The effects of acute and chronic mirtazapine treatment on 5-HT neurotransmission have been directly studied in electrophysiologic experiments. The firing of hippocampal neurons is reduced by the application of 5-HT, and this effect is reversed by the experimental drug WAY100635, a specific inhibitor of 5-HT<sub>1A</sub> receptors. Under normal conditions, hippocampal neurons are not tonically inhibited by 5-HT in anesthetized rats, so WAY100635 does not increase the firing of hippocampal neurons. However, after 21 days of paroxetine or mirtazapine administration, WAY100635 does increase hippocampal cell firing, suggesting that 5-HT neurotransmission is enhanced by chronic antidepressant treatment as expected. However, only mirtazapine was able to enhance WAY100635-induced inhibition of hippocampal firing after subacute (2 days) administration.<sup>24</sup> This phenomenon may underlie, in part, the more rapid onset of therapeutic action of mirtazapine compared with SSRIs. Interestingly, the effects of mirtazapine and paroxetine were additive on the enhancement of 5-HT neurotransmission after a 21-day treatment, an effect that appears to be paralleled by clinical studies showing the greater efficacy of paroxetine combined with mirtazapine.<sup>24</sup>

## CONCLUSION

In summary, the control of neurotransmission is a balance between a number of factors such as neuronal firing rate and the sensitivity of presynaptic autoreceptors and heteroreceptors. Table 2 shows the individual effects of antidepressants on 5-HT and NE neurotransmission, and, since the antidepressant response may involve both neurotransmitters, a composite of their overall effect on both neurotransmitters represents a viable working hypothesis. As Table 2 indicates, mirtazapine and venlafaxine have, overall, a greater effect on neurotransmission in 5-HT and NE systems. Our research suggests that antidepressants that have an enhancing action on both 5-HT and NE neurotransmission may have a more rapid or more efficacious therapeutic action than antidepressants that act on only one neurotransmitter system. This is particularly the case if the tolerability of the drugs is sufficiently good that pharmacologically significant levels can be achieved early in treatment.

The biological substrate for this more rapid onset of action may lie in the fact that many forebrain structures believed to be involved in depression are endowed with both 5-HT and NE receptors and that these neurotransmitter systems are intimately linked by negative feedback mechanisms at the presynaptic level. Mirtazapine can directly interfere with these inhibitory neuronal elements rather than awaiting their desensitization as a result of increased neurotransmitter availability in the synapse; it is conceivable that this property may account for the

more rapid onset of action of mirtazapine proposed from different methodological approaches.

*Drug names:* desipramine (Norpramin and others), mirtazapine (Remeron), paroxetine (Paxil), prazosin (Minipress and others), venlafaxine (Effexor).

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