Potential Mechanisms of Action of Atypical Antipsychotic Medications in Treatment-Resistant Depression and Anxiety

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The serotonin (5-HT) and norepinephrine neurons have reciprocal interactions at the level of their cell bodies and nerve terminals. As an illustration of such connections, selective serotonin reuptake inhibitors (SSRIs) gradually enhance serotonin transmission not only in the forebrain but also in the locus ceruleus, thereby decreasing norepinephrine neuronal firing. In contrast, blocking 5-HT_{2A} receptors in the presence of serotonin reuptake inhibition using the experimental compound YM992 enhances both serotonin and norepinephrine release. The latter pharmacologic effect may be a main contributor to the robust antidepressant effect of adding atypical antipsychotics in SSRI-resistant patients. In obsessive-compulsive disorder, risperidone has consistently been reported to be an effective augmentation strategy in SSRI-resistant patients. This effect may result in part from its antagonistic actions on dopaminergic receptors and α_2-adrenoceptors on serotonin terminals.

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The treatment of major depression is plagued with a low success rate, even when treating a first episode with an antidepressant medication at an adequate dose for a sufficient time. Remission is achieved in less than 50% of patients, perhaps in only a third of the cases if the criterion is a full recovery without residual symptoms.[1] Whereas switching medications is a conservative approach allowing the use of a single drug, it requires the same treatment duration as a first trial. In contrast, adding a second agent permits the patient to at least maintain the gains achieved, to avoid an elimination period that may produce discontinuation phenomena, and to choose a drug that may have an advantage for specific symptom relief and that may produce a rapid antidepressant action. Although the efficacy of some of these strategies has been documented in randomized double-blind trials, other approaches still lack this level of evidence and are supported only by case series and open-label studies.

There is now considerable evidence for the beneficial action of combining atypical antipsychotic drugs with selective serotonin reuptake inhibitors (SSRIs) in depression, whether it be of the unipolar or bipolar subtype.[2–10] It is important to emphasize that this strategy is effective in depressed patients without psychotic symptoms and that regimens that include doses lower than those commonly used in treating schizophrenia are generally sufficient. Therefore, these drugs could act in depression by mechanisms different from those mediating their antipsychotic effect. This review will first summarize the mechanisms of action of selective and dual reuptake inhibitors for serotonin (5-hydroxytryptamine; 5-HT) and norepinephrine (NE). In the review of the effects of these medications, there will be particular emphasis on the reciprocal interactions between these 2 systems. The neurochemical properties of the atypical antipsychotics possibly accounting for their beneficial action in treatment-resistant depression and anxiety will then be examined.

IMPACT OF SSRIs ON 5-HT AND NE TRANSMISSION

Acute administration of SSRIs initially suppresses the firing activity of 5-HT neurons because the impact of blocking 5-HT transporters is greatest in the raphe nuclei, where the density of 5-HT is the greatest in the brain.[11] This suppression results in increased activation of 5-HT_{1A} autoreceptors on the cell body of 5-HT neurons, in turn exerting a negative feedback action on their firing activity (Figure 1). This increased activation of 5-HT_{1A} autoreceptors and resulting negative feedback occur because the

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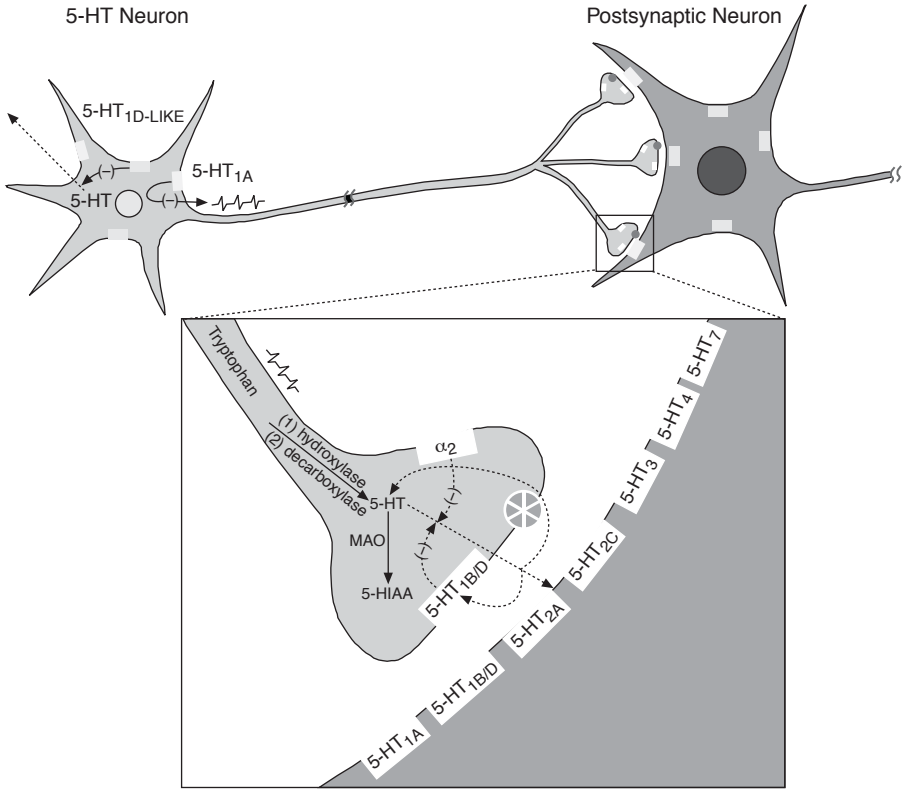
Figure 1. Diagram of the Serotonin (5-HT) System Representing the Cell Body of a 5-HT Neuron in a Raphe Nucleus of the Brainstem and Its Projections to a Target Neuron[a]

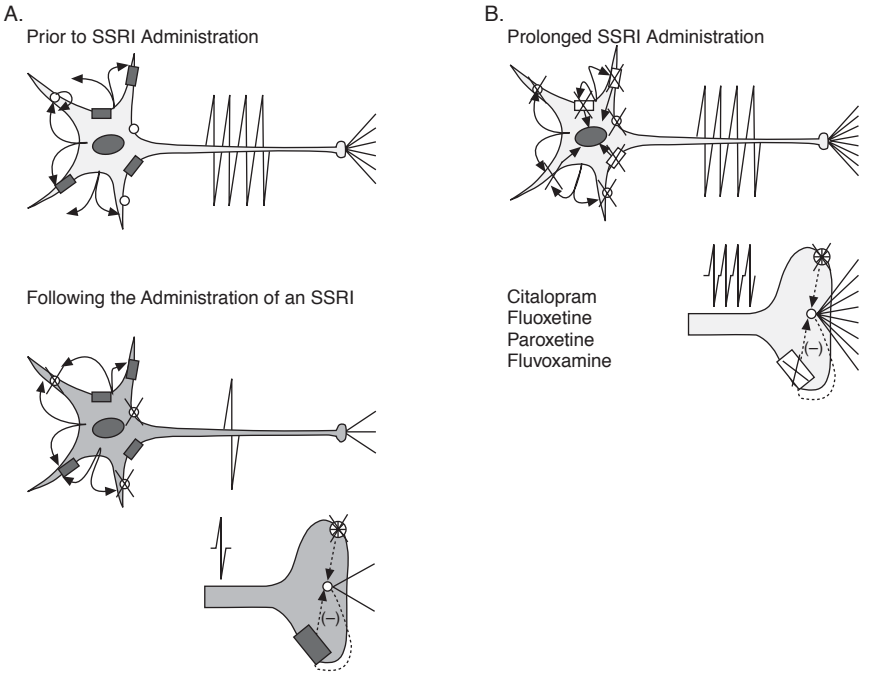


[a]The firing rate of the 5-HT neuron is represented by the 3 action potentials at the emergence of the axon from the cell body and to the left of the synaptic terminal in the enlarged caption. The cogwheels on the cell body and terminal represent the 5-HT transporters. The minus signs in parentheses within the 5-HT neuron represent an inhibitory action. Not all subtypes of postsynaptic 5-HT receptors are depicted on the postsynaptic neuron.
Abbreviations: 5-HIAA = 5-hydroxyindoleacetic acid (the main metabolite of 5-HT), MAO = monoamine oxidase.

firing rate of 5-HT neurons is generally proportional to 5-HT release throughout the brain. In projection areas, there is also an increase in the synaptic availability of 5-HT due to reuptake inhibition, but this enhanced 5-HT level is limited by the suppression of the firing activity of 5-HT neurons (Figure 2A). However, with prolonged treatment, the spontaneous firing of 5-HT neurons gradually returns to normal because of a desensitization of the 5-HT_{1A} autoreceptors (Figures 2B and 3). After a 2- to 3-week administration period, terminal 5-HT_{1B} autoreceptors also desensitize, allowing more 5-HT to be released per action potential reaching 5-HT terminals (Figure 2B). In the hippocampus, a brain structure playing an important role in the antidepressant response, the main postsynaptic 5-HT receptors mediating the effect of 5-HT (the 5-HT_{1A} receptors) do not desensitize. The attenuated responsiveness of 5-HT_{1A} and 5-HT_{1B} autoreceptors taking place in the presence of sustained 5-HT reuptake inhibition therefore leads to an increase in 5-HT neurotransmission. That such an increase mediates the antidepressant effect of these drugs is indicated by the rapid relapse of symptoms in SSRI-responsive depressed patients undergoing a dietary 5-HT depletion paradigm, which robustly decreases 5-HT synthesis.[12–14]

Sustained SSRI administration also enhances 5-HT transmission to NE neurons of the locus ceruleus. This enhanced transmission is indicated by a marked suppression of the firing activity of these neurons resulting from an enhanced inhibitory tone exerted by 5-HT. Such an attenuation of firing has been reported using paroxetine, citalopram (Figure 4A), and, more recently, fluoxetine.[15–17] This inhibitory effect is, however, indirect. It is mediated by increased activation of excitatory 5-HT_{2A} receptors on inhibitory γ-aminobutyric acid (GABA) interneurons, in turn suppressing the firing of NE neurons (Figure 5).[18] This attenuation of noradrenergic firing could explain in part the anxiolytic effect of SSRIs. However, if depressed patients do not respond to an SSRI regimen or have residual fatigue or asthenia, the decreased noradrenergic tone may account for this clinical presentation. Indeed, such a condition would be akin to the adverse effect profile of the antihypertensive agent clonidine, an α_2-adrenergic

Figure 2. Diagrams of Serotonin (5-HT) Neurons Representing Their Response and Adaptations to the Inhibition of the Activity of the 5-HT Transporters[a]



[a]The filled rectangles in *A* represent autoreceptors, and the empty ones in *B* depict them in their desensitized state. The lines represent the release of 5-HT occurring both at the cell body and at terminals of 5-HT neurons. The X's over the small circles depict the inhibition of the activity of the transporters by selective serotonin reuptake inhibitors (SSRIs). Prolonged administration is a period of 2 to 3 weeks of sustained administration to rats using osmotic minipumps implanted subcutaneously to achieve levels of drug similar to those achieved in patients.

agonist known to decrease the firing activity of locus ceruleus NE neurons.[19]

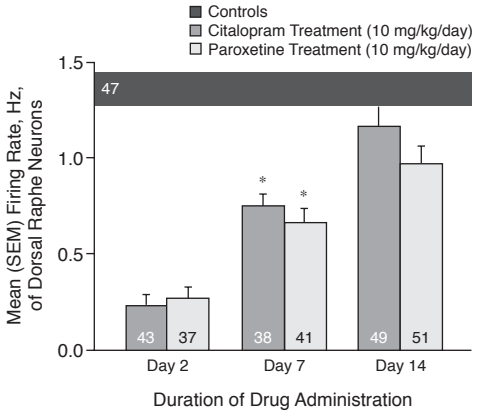
Administration of SSRIs also decreases the firing rate of dopamine neurons, but to a much smaller extent than that of NE neurons.[20] The general clinical implication of this phenomenon is thus of questionable significance. Perhaps in patients with a low dopaminergic reserve, this phenomenon could explain extrapyramidal symptoms occasionally reported with SSRI use.[21]

IMPACT OF NE REUPTAKE INHIBITORS ON THE NE AND 5-HT SYSTEMS

Acute administration of selective NE reuptake inhibitors (NRIs) decreases the firing rate of NE neurons in the locus ceruleus, the main source of NE projections in the forebrain.[22] This decrease results from the inhibition of NE transporters on the cell body of NE neurons, leading to an accumulation of synaptic NE in the vicinity of α_2-adrenergic autoreceptors, which exert a negative feedback action on NE neuronal firing (Figure 6). In projection areas, NE availability may also be enhanced after such acute NE reuptake inhibition.[23] With prolonged treatment and in the presence of NE reuptake inhibition, the firing rate of NE neurons does not recover, because their cell body α_2-adrenergic autoreceptors do not desensitize (Figure 7).[22] This is also the case with prolonged administration of monoamine oxidase (MAO) inhibitors.[24] In contrast, their counterparts on NE terminals, which are also of the α_2-adrenergic subtype, can desensitize, as documented in some but not all studies.[25–28] Some of the latter negative results may, however, be attributable to methodological issues or erroneous interpretation of the results. Most importantly, all these studies consistently show that sustained NE reuptake (and MAO) inhibition leads to a marked increase in the synaptic availability of NE.[29] The absence of recovery of the firing activity of the neurons of origin provides physiologic evidence for the lack of significant desensitization of the cell body α_2-adrenergic autoreceptors.[25,26] Such a sustained diminution of the firing rate of NE neurons during sustained reuptake inhibition thus stands in contrast with the return to normal of the firing of 5-HT neurons occurring during sustained 5-HT reuptake inhibition (Figures 3 and 8).

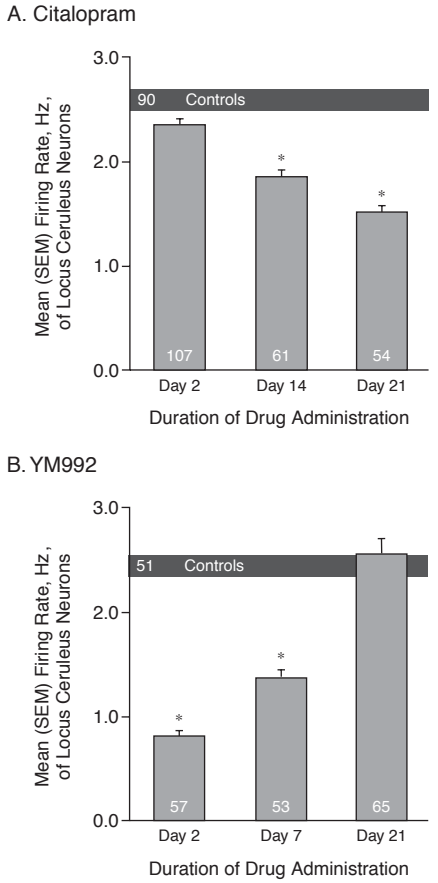
Given the enhanced level of synaptic NE achieved with sustained NE reuptake inhibition, it is thus likely that NE transmission is increased at postsynaptic α-adrenergic receptors because these do not desensitize, whereas transmission at β-adrenoceptors may be decreased because these

Figure 3. Histograms Illustrating the Spontaneous Firing Activity of Serotonin (5-HT) Neurons Recorded in the Brain of Anesthetized Rats[a,b]



[a]N. Haddjeri, P. Blier, unpublished observations, 1999.
[b]The horizontal rectangle represents the range of firing rates of 5-HT neurons in rats that received saline for various durations. The numbers within the histograms represent the number of neurons recorded in each group. Note the marked suppression of firing occurring at 2 days of treatment followed by the gradual recovery over time.
*p < .05 vs. controls, analysis of variance.

Figure 4. Histograms Illustrating the Spontaneous Firing Activity of Norepinephrine (NE) Neurons of the Locus Ceruleus Recorded in the Brain of Anesthetized Rats After Administration of (A) Citalopram and (B) YM992[a]



[a]The horizontal rectangles represent the range of firing rates of NE neurons in rats that received saline for various durations. The numbers within the histograms represent the number of neurons recorded in each group. Citalopram is a selective serotonin reuptake inhibitor, and YM992 is a selective serotonin reuptake inhibitor and a 5-HT_{2A} receptor antagonist. Note the totally opposite effects of these 2 drugs on the firing activity over a 3-week period.
*p < .05 vs. controls, analysis of variance.

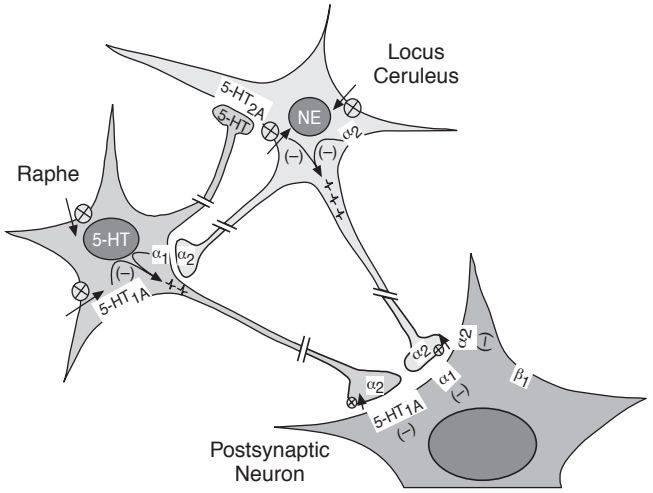
excitatory receptors desensitize during long-term NE reuptake inhibition.[30,31]

Even if antidepressant drugs such as desipramine and reboxetine are selective for the NE reuptake transporters, they do have an impact on 5-HT transmission. Prolonged administration of these drugs desensitizes α_2-adrenergic receptors present on 5-HT terminals (Figures 1 and 5).[32] These presynaptic adrenoceptors on 5-HT terminals exert an inhibitory influence on 5-HT release that is as important as the effect of 5-HT_{1B} autoreceptors.[33] Furthermore, their responsiveness is decreased in the presence of an SSRI.[34] Consequently, it is not surprising that sustained reboxetine administration leads to an increased synaptic availability of endogenous 5-HT in the rat hippocampus.[35] These results again emphasize the important interactions between the NE and 5-HT systems. It is unlikely that this increased 5-HT tone explains the antidepressant action of NRIs because 5-HT depletion generally does not produce a relapse of symptoms in NRI-responsive patients.[13] Nevertheless, it may still exert a facilitatory action on the antidepressant response.

IMPACT OF DUAL REUPTAKE INHIBITORS ON 5-HT AND NE NEURON FUNCTIONS

The effects of acute and sustained administration of nontricyclic dual reuptake inhibitors on the 5-HT and NE systems have been studied. Namely, venlafaxine, duloxetine, and milnacipran have been investigated.[36–40] In the case of venlafaxine and duloxetine, their potencies to inhibit acutely the firing activity of either 5-HT or NE neurons are not decreased when assessed in the presence of a lesion of the other type of neurons.[36,41] Such results therefore confirm that reuptake transporters represent the main determinant in the modulation of the synaptic availability of these neurotransmitters in the immediate cell body surroundings. In contrast, the inhibitory action of milnacipran on 5-HT neuronal firing is lost when NE neurons are lesioned, indicating that this drug is a much more potent modulator of NE neuron activity than that of 5-HT neurons. Acute injections of such drugs in microdialysis experiments have largely confirmed that they can inhibit 5-HT and NE transporters to a significant extent, as shown by an increase in the extracellular levels of these neurotransmitters in postsynaptic areas.[42]

Figure 5. Diagram Illustrating the Various Receptors Controlling the Function of Serotonin (5-HT) and Norepinephrine (NE) Neurons Both at the Level of Their Cell Body and at Terminals[a]



[a]The cogwheels on the cell body and terminal represent the 5-HT and NE transporters, present on each respective type of neuron. The minus signs in parentheses within the neurons represent an inhibitory action and the plus signs, an excitatory action. The 5-HT_{2A} receptor presented on the cell body is actually located on a γ-aminobutyric acid interneuron.

Sustained administration of venlafaxine and of duloxetine produces similar adaptive changes of 5-HT neuronal firing as for SSRIs. Prolonged administration of venlafaxine in a regimen that inhibits both 5-HT and NE transporters results in a prompt and sustained attenuation of NE neuron firing, as is seen with NRIs. In projection areas, it has sometimes been difficult to obtain consistent changes in overall 5-HT or NE transmission using these drugs, possibly resulting from the difficulty in obtaining potent and sustained reuptake inhibition in the rat due to its rapid elimination. Nevertheless, venlafaxine and duloxetine were at least observed to increase 5-HT transmission in the hippocampus.

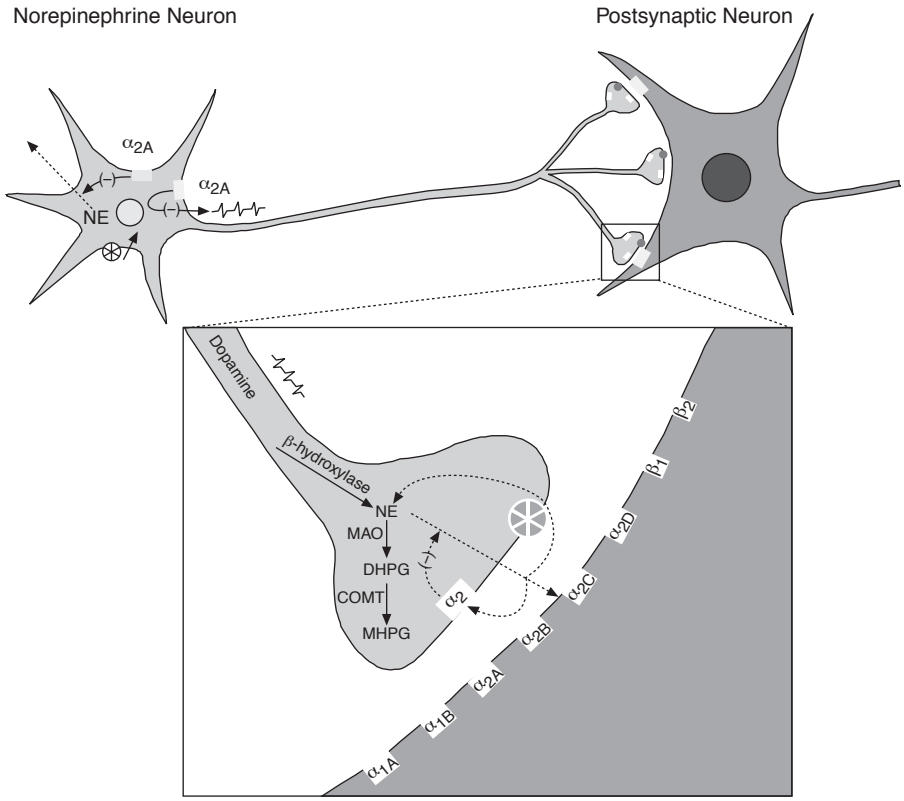
PROPERTIES OF ATYPICAL ANTIPSYCHOTICS POSSIBLY ACCOUNTING FOR THEIR POTENTIAL THERAPEUTIC ACTION IN DEPRESSION

The antagonism of dopamine type 2 (D_2) receptors per se is not likely to contribute to the antidepressant action of the strategy of augmenting antidepressant therapy by adding treatment with atypical antipsychotic medications in depression, as the selective D_2 antagonist haloperidol is not considered useful in depression when psychotic symptoms are not present. In contrast, atypical antipsychotics share the property of effectively blocking 5-HT_{2A} receptors, more potently so than D_2 receptors, by definition.[43] Although selectively blocking this receptor subtype may contribute to a mild antidepressant action, as evidenced by the clinical action of the 5-HT_2 antagonist ritanserin,[44,45] it is unlikely that it could explain the robust therapeutic action of atypical antipsychotics in depression. In contrast, potent blockade of the 5-HT_{2A} receptor subtype in the presence of reuptake inhibition of 5-HT produced initially unsuspected biological actions.[46,47] These actions are obviously due to interactions between the 5-HT and the NE systems, as discussed above. Acute injections of an SSRI with atypical antipsychotics can indeed increase the extracellular levels of 5-HT, NE, and even dopamine, as assessed in microdialysis experiments carried out in the forebrain.[48]

To determine if 5-HT_{2A} receptor antagonism could possibly account for the additional benefits of combining an SSRI with an atypical antipsychotic, the effects of acute and sustained administration of YM992 were studied on the 5-HT and the NE systems in the rat brain.[46,49] This experimental compound is an SSRI/5-HT_{2A} antagonist.[50] With regard to its effects on 5-HT neurotransmission, there was no difference between the action of this drug when compared with actions produced by SSRIs such as citalopram, paroxetine, fluoxetine, or fluvoxamine.[10] YM992 increased 5-HT transmission by desensitizing 5-HT_{1A} autoreceptors in the dorsal raphe and 5-HT_{1B} autoreceptors in the hippocampus, thereby increasing 5-HT release in the presence of 5-HT reuptake inhibition to produce a greater activation of normosensitive postsynaptic 5-HT_{1A} receptors in that brain structure.[49]

In contrast, the effect of YM992 on NE neuronal firing activity was drastically different from that of SSRIs and even NRIs and MAO inhibitors.[22,24,46] Surprisingly, however, it exerts a robust inhibitory action on the firing of these neurons after 2 days of sustained administration (Figure 4B). To determine whether this attenuation of firing was due to an increased activation of α_2-adrenoceptors

Figure 6. Diagram of the Norepinephrine (NE) System Representing the Cell Body of an NE Neuron of the Locus Ceruleus Nucleus in the Pons and Its Projections to a Target Neuron[a]



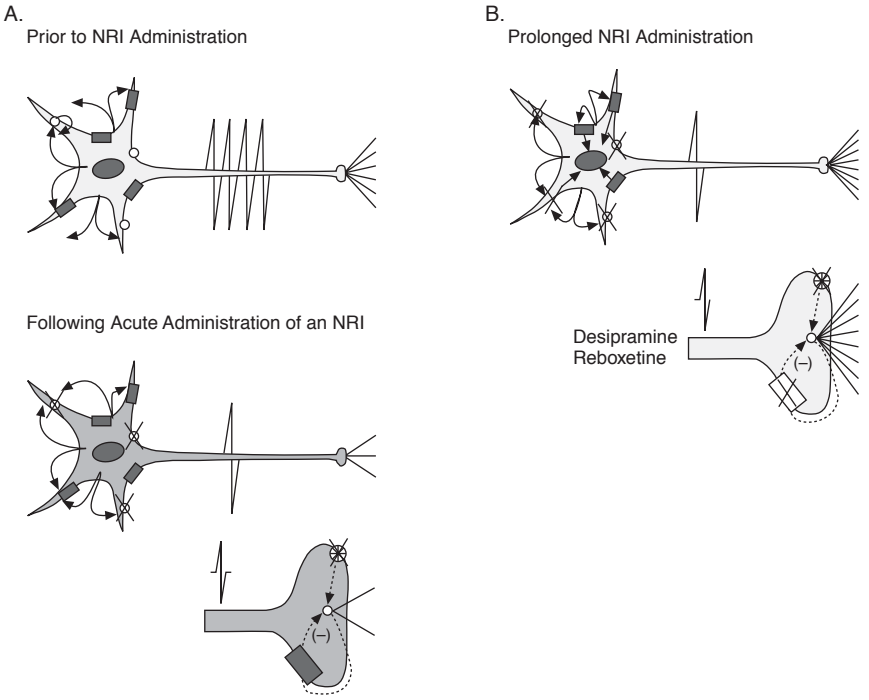
[a]The firing rate of the NE neuron is represented by the 3 action potentials at the emergence of the axon from the cell body and to the left of the synaptic terminal in the enlarged caption. The cogwheels on the cell body and terminal represent the NE transporters. The minus signs in parentheses within the NE neuron represent an inhibitory action.
Abbreviations: COMT = catechol *O*-methyltransferase, DHPG = 3,4-dihydroxyphenylglycol, MHPG = 3-methoxy-4-hydroxyphenylglycol, MAO = monoamine oxidase.

on the cell body of NE neurons by endogenous NE, the effect of the α_2-adrenoceptor antagonist idazoxan was examined in rats treated for 2 days with YM992.[46] Idazoxan reversed the inhibitory action of YM992 on the firing of NE neurons and actually brought this parameter to the same level as that in control rats. This observation indicates that the suppression of firing produced by a 2-day regimen of YM992 was entirely attributable to an increased concentration of NE, which activated α_2-adrenergic autoreceptors. In fact, microdialysis experiments in the rat frontal cortex also show an enhancement of NE levels after acute injection of YM992.[47]

Upon prolonging the administration of YM992 over a 3-week period, NE neurons gradually recovered their normal firing rate (Figure 4B), in contrast to the effects of NRIs and MAO inhibitors, which produce a sustained attenuation of this spontaneous neuronal activity. The recovery was due to the desensitization of the cell body α_2-adrenergic autoreceptors because the responsiveness of NE neurons to the α_2-adrenergic agonist clonidine was markedly attenuated. This adaptive alteration thus stands in sharp contrast to the lack of desensitization after long-term administration of NRIs and MAO inhibitors.

The effects of SSRIs and that of YM992 on NE neuronal firing are thus diametrically opposed. Such results indicate that sustained administration of an SSRI/5-HT_{2A} antagonist would not dampen the noradrenergic tone as SSRIs do. To the contrary, enhanced NE transmission would most likely result from the use of such combined actions, assuming that enhanced NE release is maintained with treatment prolongation. It is therefore conceivable that the beneficial action of atypical antipsychotics when used with SSRIs may be due to their action on NE neurons, somehow from a cascade effect resulting from 5-HT_{2A} receptor blockade. In support of this possibility is the observation that acute intravenous injection of olanzapine reverses the fluoxetine-induced suppression of firing of NE neurons after a long-term treatment.[17] The exact biological basis for this synergy is currently unknown. Nevertheless, it is important to emphasize again that NE neurons do not have 5-HT_{2A} receptors (Figure 5).[51] There is, however, an important population of excitatory 5-HT_{2A}

Figure 7. Diagrams of Norepinephrine (NE) Neurons Representing Their Response and Adaptations to the Inhibition of the Activity of the NE Transporters[a]



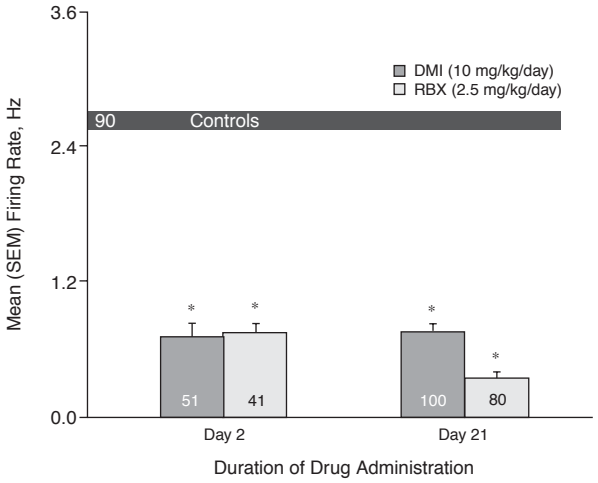
[a]The lines represent the release of NE occurring both at the cell body and at terminals of NE neurons. The X's over the small circles depict the inhibition of the activity of the transporters by selective norepinephrine reuptake inhibitors (NRIs). The filled rectangles in *A* represent autoreceptors, and the empty one in *B* depicts an autoreceptor in its desensitized state on the terminal only. Prolonged administration is a period of 2 to 3 weeks of sustained administration to rats using osmotic minipumps implanted subcutaneously to achieve levels of drug similar to those achieved in patients.

receptors on GABA neurons that provide an inhibitory tone on NE neurons in the presence of 5-HT reuptake inhibition.[18]

IS THERE A ROLE FOR α_2-ADRENERGIC RECEPTOR ANTAGONISM IN THE ANTIDEPRESSANT EFFECT OF ATYPICAL ANTIPSYCHOTICS?

Risperidone has a high affinity for α_2-adrenergic receptors, which is about the same as its affinity for D_2 receptors.[52] It is thus possible that this atypical antipsychotic could increase the synaptic availability of NE transmission by blocking the inhibitory influence of cell body α_2-adrenergic autoreceptors, thereby enhancing NE neuronal firing. Norepinephrine release could also be increased because of a direct action of risperidone at the level of NE terminals resulting from its inhibitory action on α_2-adrenergic autoreceptors in projection areas. Finally, risperidone could contribute to enhancing 5-HT release through blockade of α_2-adrenergic receptors on 5-HT terminals (Figure 5). In this respect, risperidone and mirtazapine both share the capacity to antagonize these 3 populations of α_2-adrenergic receptors, as well as being potent 5-HT_2 receptor antagonists.[52,53] Theoretically, risperidone could act as an antidepressant agent used on its own. Similarly, quetiapine is expected to block quite efficiently α_2-adrenergic receptors because its second highest affinity is toward this receptor subtype, after that for histamine type 1 receptors.[52] As predicted from the former biochemical property, systemic administration of quetiapine enhances the extracellular concentration of NE in the rat cerebral cortex.[54] It is indeed greater than that for 5-HT_{2A} and D_2 receptors. In contrast, olanzapine is devoid of affinity for α_2-adrenergic receptors, and it is an effective augmentation agent in treatment-resistant depression. On the one hand, the lack of affinity of olanzapine for α_2-adrenoceptors casts some doubt on the possibility that the antagonism of these receptors could provide additional benefit in patients with treatment-resistant depression. In support of this is the equal effectiveness of the addition of risperidone and olanzapine to SSRI-resistant patients in a recent head-to-head double-blind trial.[55] On the other hand, it is conceivable that a patient who does not respond to the addition of olanzapine may have a favorable response to another atypical antipsychotic endowed with an α_2-adrenergic antagonistic property, given the pronounced effect that this receptor can exert on NE and 5-HT transmission.

Figure 8. Histograms Illustrating the Spontaneous Firing Activity of Norepinephrine (NE) Neurons Recorded in the Brain of Anesthetized Rats[a]



[a]The horizontal rectangle represents the range of firing rates of NE neurons in rats that received saline for various durations. Note the marked and sustained suppression of firing occurring at 2 and 21 days of treatment. The numbers within the histograms represent the number of neurons recorded in each group.
*p < .05 vs. controls, analysis of variance.
Abbreviations: DMI = desipramine, RBX = reboxetine.

EFFECTS OF ATYPICAL ANTIPSYCHOTICS ON NEUROGENESIS

A recent theory proposed to account for the antidepressant response is increased production of new neurons in critical brain areas such as the hippocampus.[56] Given the resurgence of depressive symptoms within a few hours in formerly ill patients when undergoing a tryptophan depletion paradigm, and their subsequent prompt recovery when restored to a normal diet,[11,13] it is therefore unlikely that this enhanced neurogenesis would account for the antidepressant response. Logically, such a phenomenon would, in contrast, better explain the maintenance of the antidepressant response when successfully stopping a medication after prolonged treatment. In this regard, it is important to mention that atypical antipsychotics do promote neurogenesis.[57–59] Nevertheless, the combined action of atypical antipsychotics and SSRIs does not provide an additional effect on neurogenesis,[59] which again underscores the likely important role of enhanced monoaminergic transmission in the potentiating action of atypical antipsychotics in treatment-resistant depression.

PUTATIVE ADDITIONAL ACTIONS OF ATYPICAL ANTIPSYCHOTICS IN TREATMENT-RESISTANT DEPRESSION

Microdialysis studies carried out in the brain of laboratory animals have shown that atypical antipsychotics enhance dopamine levels in the frontal cortex.[54,60] Because these drugs antagonize D_2 receptors, but not D_1 receptors to a similar extent, this increased level of dopamine could augment the degree of activation of the D_1 receptor family. Atypical antipsychotics are generally believed to improve cognitive functions in patients with schizophrenia through this mechanism. It is thus possible that they could contribute as well to the antidepressant response via this mechanism in the forebrain.

Sleep architecture is generally perturbed in depression. Common alterations are decreases in the rapid eye movement latency and of deep stages of sleep, that is, stages 3 and 4. Atypical antipsychotics increase these parameters.[61–64] In contrast, SSRIs decrease them, as well as increasing the number of awakenings during the night.[65] Consequently, the use of atypical antipsychotics in treatment-resistant depression, beyond helping patients sleep better, may also act in part by reestablishing such deep stages of sleep that are considered to exert a restoring action on bodily functions.

PUTATIVE MECHANISMS OF ACTION OF ATYPICAL ANTIPSYCHOTICS IN ANXIETY DISORDERS

Anxiety is often present in major depression, and, because 5-HT and NE strategies are used to treat depression, anxiety symptoms generally abate as well. Consequently, there must be some overlap in the neurobiological mechanisms responsible for the antidepressant and anxiolytic responses. Therefore, potentiating 5-HT and NE transmission in SSRI-resistant patients may produce a beneficial action in some anxiety disorders, as in generalized anxiety disorder with the dual reuptake inhibitor venlafaxine or in posttraumatic stress disorder with a low-dose atypical antipsychotic. One exception, however, would be obsessive-compulsive disorder (OCD). In this disorder, noradrenergic strategies are not effective per se and adding such an agent is not of significant utility.[66]

The mechanism by which SSRIs produce their anti-OCD action is thought to result from increasing 5-HT transmission in the orbitofrontal cortex, mainly through desensitization of the terminal 5-HT autoreceptors.[67] In brief, there is a hyperactivity in that structure and in a neuronal loop to the head of the caudate nucleus, the basal ganglia, the thalamus, and back to the orbitofrontal cortex in OCD.[68] Long-term SSRI administration would dampen this hyperactivity through an enhanced inhibitory action exerted by 5-HT mainly in the orbitofrontal cortex. This adaptation takes much longer to develop than in depression-related brain structures. It also requires higher-dose regimens of SSRIs. These parameters of SSRI administration correspond to those effective in OCD, that is, longer duration of treatment and higher doses in OCD than in depression. Interestingly, repeated electroconvulsive shocks, which remain a standard in depression and increase 5-HT

transmission in the hippocampus, do not enhance 5-HT release in the orbitofrontal cortex and are not effective in pure OCD.[67]

Risperidone has consistently been reported to be effective in treatment-resistant OCD, including positive results in 3 double-blind studies.[69–71] Results with the addition of olanzapine are not as consistent, with 1 negative and 1 positive double-blind trial.[72,73] The addition of quetiapine has produced at least 1 double-blind positive study.[74] One possibility for the beneficial action of the addition of risperidone and quetiapine in SSRI-resistant patients may be their capacity to block α_2-adrenoceptors on 5-HT terminals at low doses.[52] In such a pharmacologic condition, 5-HT autoreceptors would presumably be desensitized by the prior SSRI treatment and the other main negative feedback element on 5-HT terminals, the α_2-adrenergic heteroreceptors (Figure 1), would be rendered ineffective, thereby removing this remaining inhibitory action on 5-HT release.

It may appear paradoxical that atypical antipsychotics are antagonists for an important 5-HT receptor, the 5-HT_2 receptor, in the cortex, yet some of them would exert their beneficial action in OCD by enhancing 5-HT transmission. Such 5-HT_2 receptors in the orbitofrontal cortex have, however, different properties in that drugs such as risperidone and ritanserin at low doses block a physiologic 5-HT_2 response in the medial prefrontal cortex but not in the orbitofrontal cortex.[75] These observations in laboratory animals would be consistent with the effectiveness of low doses of risperidone in OCD because 5-HT_2 receptors would not be significantly blocked in the orbitofrontal cortex. In contrast, high doses of risperidone begin to antagonize 5-HT_2 responses in the orbitofrontal cortex, and high doses of atypical antipsychotics may exacerbate OCD, or even trigger it in patients with schizophrenia.

CONCLUSIONS

There is now considerable evidence supporting the use of low-dose atypical antipsychotics in treatment-resistant depression. In-depth evaluations of the neurobiological effects of this strategy have revealed robust effects in enhancing the availability of catecholamines, mostly NE, through complex interactions between monoaminergic systems. Given that these drugs exert their beneficial action in depression at regimens that would be subtherapeutic for most patients with schizophrenia, it appears that the term *atypical antipsychotic* inadequately describes their therapeutic potential in mood and even anxiety disorders.[69]

This second generation of medications for the treatment of psychoses carries a much smaller risk of inducing permanent motor control dysfunctions, such as tardive dyskinesia. Using them at lower doses for treating mood and anxiety disorders than are used for treating schizophrenia may increase their safety margin in this regard. It remains to be determined, however, if the risk of using such agents in this manner carries a lower risk with regard to hyperglycemia and hyperlipemia. Nevertheless, they should be considered as pharmacologic tools in their clinical action in mood and anxiety disorders rather than as antipsychotics per se. A more proper denomination could be *anxiothymic regulators*. Given their reported effectiveness in such conditions, safety considerations, and the relatively short track record of their use in treatment-resistant depression, it would still be prudent to consider atypical antipsychotics not as first-line agents but as a second-line augmentation strategy in mood disorders.

Drug names: citalopram (Celexa and others), clonidine (Duraclon, Catapres, and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), haloperidol (Haldol and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, olanzapine, quetiapine, risperidone, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of obsessive-compulsive disorder or depression.

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