Central dopaminergic and noradrenergic systems play essential roles in controlling several forebrain functions. Consequently, perturbations of these neurotransmissions may contribute to the pathophysiology of neuropsychiatric disorders. For many years, there was a focus on the serotonin (5-HT) system because of the efficacy of selective serotonin reuptake inhibitors (SSRIs), the most prescribed antidepressants in the treatment of major depressive disorder (MDD). Given the interconnectivity within the monoaminergic network, any action on one system may reverberate in the other systems. Analysis of this network and its dysfunctions suggests that drugs with selective or multiple modes of action on dopamine (DA) and norepinephrine (NE) may have robust therapeutic effects. This review focuses on NE-DA interactions as demonstrated in electrophysiological and neurochemical studies, as well as on the mechanisms of action of agents with either selective or dual actions on DA and NE. Understanding the mode of action of drugs targeting these catecholaminergic neurotransmitters can improve their utilization in monotherapy and in combination with other compounds particularly the SSRIs. The elucidation of such relationships can help design new treatment strategies for MDD, especially treatment-resistant depression.

Introduction

Given that the therapeutic efficacy of the tricyclic drugs was based on their ability to inhibit norepinephrine (NE) and serotonin (5-HT) transporters, the role of brain 5-HT and NE neurotransmissions in the mechanism of action of antidepressant drugs prompted extensive studies [1–4]. Dopamine (DA) on the other hand, despite evidence of its involvement in the action of certain antidepressants, attracted less attention [5]. First, reserpine which depletes catecholamines (NE, DA, and epinephrine) results in lowering mood; second, the monoamine oxidase inhibitors (MAOIs), which increase the synaptic availability of catecholamines, have clinical efficacy in depression [6,7]. Furthermore, it was reported that the catecholamine synthesis inhibitor α-methylparatyrosine produced a resurgence of depressive symptoms in patients improved by the NE reuptake inhibitor (NRI) desipramine, but not by the SSRI fluoxetine [8]. This suggests that not all antidepressants work via a single monoamine-related mechanism. While dietary depletion of the DA precursors phenylalanine and tyrosine does not result in the relapse of formerly depressed patients off their medication [9], an inhibition of tyrosine hydroxylase by α-methylparatyrosine decreases catecholamine metabolites levels and induces a worsening of depressive symptoms in patients being treated with catecholamine reuptake inhibitors [8]. The fact that pure dopaminergic drugs, such as pramipexole, are effective antidepressants suggests that enhancing DA function may underlie, at least in part, a therapeutic response in major depressive disorder (MDD) [10,11].

Mounting evidence indicates that acting on different systems may have a greater therapeutic effect in depression [12,13]. Understanding the relationship between the NE and DA systems, and how therapeutic drugs modulate them, may open new avenues to treat depression, particularly treatment-resistant depression.
DA Modulation of the Noradrenergic Transmission

Although retrograde tracer studies showed few projections from ventral tegmental area (VTA) neurons to the locus coeruleus (LC) [14,15], dense expression of D_{2/3} mRNA and high density of binding sites using [^{125}I]iodosulpiride have been documented [16–19]. Further evidence for the projection of VTA neurons to the LC comes from the observation that the DA content of the LC is decreased following a 6-hydroxydopamine (6-OHDA) lesion of the VTA [20].

Experiments have been carried out to determine the role of DA and NE in their projection areas (Figure 1). Iontophoretic studies showed that local application of DA suppressed the firing activity of NE neurons in the LC [21–23]. Given this preponderant inhibitory role of DA input to the LC, the selective lesioning of VTA DA neurons resulted in a significant increase of the mean firing rate of LC NE neurons with a greater increase in neurons displaying bursting activities [24]. An initial study aimed at characterizing the receptor involved in this effect showed that DA has an inhibitory effect on cell firing in the LC, through stimulation of α_{2}-adrenoceptors [23]. Furthermore, the inhibitory effect of intravenously administered (+)-3-PP, a partial D_{2} receptor agonist, which was shown to inhibit substantia nigra DA neurons, was partially blocked by the α_{2}-adrenoceptor antagonist yohimbine, but not by the α_{1}-adrenoceptor antagonist prazosin, or the D_{2} receptor antagonist haloperidol [22]. Although the selective D_{2}-like receptor antagonist haloperidol has been reported to enhance the spontaneous firing activity of NE neuron in the LC [25,26], another study has shown that systemic administration of haloperidol affected neither LC NE neuronal firing nor the inhibitory action of DA [21]. Furthermore, the effectiveness of iontophoretically applied NE and DA to suppress NE neuronal firing was blocked by the α_{2}-adrenoceptor antagonist idazoxan, but not by the D_{2}-like receptor antagonist raclopride. This suggests that only α_{2}-adrenoceptors are involved in the effect of DA in the LC [21]. This type of overlap in function for DA and NE is not unexpected as the molecules differ by only one hydroxy group in the β-carbon of their side chain.

**Figure 1** Schematic representation of the reciprocal interaction between serotonin (5-HT) neurons in the dorsal raphe nucleus, norepinephrine (NE) neurons in the locus coeruleus and dopamine (DA) neurons in the ventral tegmental area. It also shows the nature of modulation of different neurotransmitters on diverse classes of auto- and heteroreceptors. (+) signs indicate an agonism or stimulatory effect and (−) signs indicate an antagonism or an inhibitory effect.
Figure 2 Illustration of the conversion of DA to NE by β-hydroxylase. Note that the difference between these two molecules resides only in one hydroxy group, thus imparting these two transmitters with only small differential three-dimensional configurations.

It is interesting that the D2/3 receptor agonist pramipexole and the catecholamine releaser bupropion significantly inhibited LC NE discharge after 2 days of sustained administration [27–29]. This effect was reported to be through stimulation of α2-adrenoceptor, since idazoxan increased LC NE neuron firing to the same level as in controls and in rats treated subcutaneously with either compound [27,29,30]. Furthermore, DA inhibits paradoxical sleep (likely through an action on NE neurons) in the LC via activation of α2-adrenoceptors since this effect was mimicked by the α2-adrenoceptor agonist clonidine and blocked by α2-adrenoceptor antagonist RX821002 [31].

Norepinephrine Modulation of the DA Transmission

Several studies using tracing techniques have shown that NE neurons in the LC project to the VTA and that immunoreactivity for NE transporters (NET) is present within the VTA region [32–36]. The presence of such projections was recently confirmed as being bilateral, but they were shown to also originate from the caudal medulla [37]. Moreover, an ultrastructural study has demonstrated that some NE terminals make close contacts onto VTA neurons [38]. Because the majority of contacts were not in direct synaptic apposition, it was suggested that most NE actions on DA neurons in the VTA are through extrasynaptic modulation. Furthermore, using quantitative autoradiography, α1-adrenoceptors have also been detected in the VTA [39] and immunoreactivity for α2C-adrenoceptors was also on DA neurons of VTA [40]. Finally, the selective NRI desipramine increased NE concentrations in VTA [41].

The lesion of the LC NE neurons, using local injection of 6-OHDA, resulted in a significant decrease in brain NE and an increase in the discharge rate of VTA DA neurons attributable to a higher number of bursts and action potentials per burst [24] (see Figure 1). Despite these results being consistent with an inhibitory action of NE on VTA DA neurons, contradictory data have also been reported. For example, systemic administration of idazoxan or the selective NRI reboxetine, which raises extracellular NE levels in the VTA [41], increased the burst firing activity of DA neurons in the VTA [42–45]. It has been demonstrated that the local application of the α2-adrenoceptor agonist clonidine in the VTA did not inhibit DA neurons [46,47]. As a result, it is unlikely that the inhibitory effect of NE involved postsynaptic α2-adrenoceptors. However, recent data from Guiard et al. [21] indicate that idazoxan attenuates the inhibitory effect of iontophoretically applied NE on VTA DA neurons. Furthermore, electrophysiological studies have shown that the D2-like receptor antagonist sulpiride prevented the inhibitory effect of NE on VTA DA neurons [46–49]. It thus seems possible that this neurotransmitter may act through activation of both α2-adrenoceptors and D2 receptors [21,46,49]. On the other hand, electrophysiological studies demonstrated that microiontophoretic application of DA in the VTA reduced the firing of DA neurons while this effect was blocked by sulpiride and also by the nonselective α-adrenoreceptor antagonist piperoxane [46]. This is concordant with results showing that DA inhibits the discharge of DA neurons by acting both on D2 and α2-adrenoceptors, since this inhibitory effect was prevented by idazoxan [21]. It is worth noting that intravenous injection of a high dose of clonidine increases both firing and burst activity of VTA DA neurons [50,51]. It is thus possible that clonidine suppressed the firing rate of NE and 5-HT neurons, as well as directly decreasing NE and 5-HT release, through action on terminal α2-adrenoceptors. Such action would remove inhibitory tones exerted by NE and 5-HT on DA neurons.
Further evidence for a synergy between NE and DA was provided by recent electrophysiological studies showing that concurrent inhibition of NE and DA reuptake with intravenous injection of nomifensine produced a complete inhibition of firing of DA neurons, whereas the selective DA reuptake inhibitor GBR12909 failed to do so. In addition, nomifensine compromises the inhibitory potential of SSRI escitalopram on 5-HT neuronal firing [52] (Figure 3). Because growing evidence demonstrates that both NE and DA exert an excitatory action on dorsal raphe nucleus (DRN) 5-HT neuronal firing [13, 53, 54], the capacity of NET and DAT to alter the inhibitory effect of SSRI escitalopram on 5-HT neuronal firing was investigated using the selective NRI reboxetine, the selective DA reuptake inhibitor GBR12909, and the dual NE and DA reuptake inhibitor nomifensine. It was found that neither pretreatment with reboxetine nor with GBR12909, at doses previously shown to elevate extracellular NE [55] or DA levels [56], respectively, attenuated the escitalopram-induced decrease in DRN 5-HT firing rates. However, when NE and DA levels were simultaneously increased by systemic administration of the dual-acting reuptake inhibitor nomifensine, an upward shift of the dose-response curve of escitalopram was observed demonstrating that both catecholamines were required to counteract the inhibitory effect of escitalopram on 5-HT neurons [52]. It was therefore concluded that when the excitatory influence of both NE and DA is enhanced, the inhibitory effect of 5-HT₁A autoreceptor on 5-HT neuronal firing is dampened. This is strengthened by the results of electrophysiological studies of the triple reuptake inhibitor SEP225289, showing that it was more
potent at inhibiting NE neurons than 5-HT neurons, despite apparent identical affinity of this compound for all three reuptake transporters [37].

**NE-DA Interactions in the Forebrain**

Several lines of evidence point out to an intricate relationship between NE and DA not only at the somatodendritic level as described above, but at the terminal areas as well. Electrophysiological interactions between NE and DA were mainly studied in the hippocampus. It was found that partial and total inhibition of CA3 pyramidal neuronal activity obtained with, respectively, iontophoretic application of DA and NE was not blocked by systemic injection of the D2 receptor antagonist haloperidol nor by local application of the D2 receptor antagonist raclopride [21]. However, as in the VTA and LC, idazoxan prevented the inhibitory effect of DA as well as NE on CA3 pyramidal cells [21]. To understand better the physiological importance of these effects, the possibility that the NE neurons themselves could be the main source of DA in the hippocampus was addressed. Indeed, the observation that the selective NRI, desipramine, but not the DA reuptake inhibitor GBR12909, prolonged the inhibitory effects of microiontophoretic applied-DA strongly suggests that the clearance of DA in the hippocampus is mediated by the NET. This is consistent with previous data showing that DA reuptake by NE terminals occurs in the prefrontal cortex (PFC), the nucleus accumbens shell, and the bed nucleus of stria terminalis [58,59]. NE and DA neurons converge in the medial PFC where NE terminals regulate DA release in this brain region. Microdialysis studies first suggested that DA in frontal cortex is elevated not only by blockade of DA uptake sites on DA terminals, but also by NET located on NE terminals [59–63], where NET is known to have a higher affinity for DA than DA transporter (DAT) [63–65]. Indeed, in the presence of blockade of NET by desipramine, GBR12909 further increased the extracellular concentrations of cortical DA [66]. Using NET knock-out mice, it was shown that DA uptake into frontal cortex synaptosomes is the result of NET and not DAT blockade, because a selective concentration of GBR12909 did not block DA uptake into frontal cortex synaptosomes from NET knock-out mice [67]. While controversial [68], it was also hypothesized that DA in the cerebral cortex may be released from noradrenergic neurons [59], since after 6-OHDA lesion of VTA, there was no change in the concentration of extracellular DA in cerebral cortex, while there was a marked decrease in the ipsilateral nucleus accumbens. Furthermore, the administration of haloperidol failed to modify extracellular levels of DA in cortex while increasing it in nucleus accumbens [69].

The PFC network activity is fundamental in processing information in the brain [70] and malfunctioning of this structure can underlie a variety of symptoms common to several psychiatric illnesses [71], including mood disorder [72]. The PFC circuits are modulated by NE and DA which play a complementary and critical role in PFC function, where their depletion has been shown to be as detrimental as removing the cortex itself [73]. The action of NE through α2A-adrenoceptors and DA through D1 receptors is key to PFC function [74–76]. These receptors regulate incoming glutamate signals at the level of dendritic spines on pyramidal cells in PFC. Indeed, these signals are sorted at the level of the head of a dendritic spine where it can pass to the apical dendrite.

In normal condition, where neurons efficiently process information, NE is released to strengthen signal detected as desirable, while in the case of neurons receiving inputs considered as noise, DA is released to weaken these inappropriate connections [77]. Under optimal neurochemical conditions, moderate levels of NE engage α2A-adrenoceptors and increase signal in form of responses to preferred special directions, whereas moderate levels of D1 receptor stimulation decrease “noise” measured as responses to nonpreferred spatial directions. PFC working memory function is improved by α2A-adrenoceptor stimulation and moderate levels of D1 receptor stimulation, but impaired by high levels of D1, α1, and β1 receptor stimulation [78,79]. Stress exposure impairs working memory function through excessive stimulation of DA and NE receptors in PFC [78]. Optimal levels of D1 stimulation appear to focus signal transmission, conveying only large or temporally coincident signals to the cell body. However, higher concentration of DA or a D1 receptor agonist effectively impedes information transfer from dendrite to soma [76,80]. This interruption of information transfer may underlie the working memory impairment seen at high levels of D1 receptor stimulation [76]. When moderate doses of atomoxetine and methylphenidate, which increase endogenous NE and DA levels in PFC [81,82] were administered, there was an improvement of PFC function via actions on α2A-adrenoceptor and D1 receptors [83,84]. PFC functioning is also improved through stimulation of postsynaptic α2A-adrenoceptors, as with guanfacine [74]. Indeed, animal studies have shown that guanfacine improves a variety of PFC functions, including working memory, response inhibition, attention regulation and conditional motor responding [78,85]. Altogether, these data indicate that NE and DA act in complementary fashion to regulate the processing of information in the PFC pyramidal cells and that this processing is improved by optimal doses of drugs.
acting on NE and DA systems, thus reducing related psychiatric symptoms.

**Single and Dual DA and NE Acting Antidepressants**

In this section, we will discuss the effects of different drugs acting on NE or DA or both, via an action on DA and/or NE receptors or transporters. Understanding the mode of action of drugs targeting these catecholaminergic neurotransmitters can improve their utilization in monotherapy and in combination with other compounds particularly the SSRIs. The elucidation of such relationships can help design new treatment strategies for MDD, especially treatment-resistant depression.

**Pramipexole**

Several antidepressants enhance DA neurotransmission [5,86] and it is interesting to examine results obtained with the D_2/D_3 receptor agonist pramipexole, a drug with no known affinity for either NE or 5-HT neuronal elements. In a randomized double-blind study, Corrigan et al. [87] showed that by week 8, patients with MDD receiving pramipexole alone had significant improvement over baseline compared to the placebo group. Several other studies reported the efficacy of pramipexole as an augmentation strategy in resistant unipolar and bipolar depression [88–93].

While subacute administration of pramipexole significantly decreases the spontaneous firing rate of VTDA neurons and the extracellular concentration of DA in striatum [27,94], sustained administration over two weeks resulted in recovery of discharge to normal level [27] (Figure 4) due to desensitization of D_2 autoreceptor [27,95] (Figure 5). While the percentage of bursts was decreased at 14 days, it was compensated by a return to the normal level of the number of bursts per minute. Restoration of firing rate of DA neurons, despite a decrease in its bursting activity, may lead to a net enhancement of the DA transmission in postsynaptic brain targets. Assessment of the tonic activation of DA receptors in postsynaptic regions is deemed crucial to confirm this possibility and is currently underway in our laboratory.

Given the reciprocal interactions between DA, NE, and 5-HT neurons, it is important to consider the effects of pramipexole on all three systems. It has been shown that short-term administration of pramipexole resulted in significant reduction of LC NE firing activity. Despite the previously reported lack of affinity of pramipexole for NE neuronal elements, this effect may still happen through a direct activation of \( \alpha_2 \)-adrenergic autoreceptors, since idazoxan effectively reversed this inhibition [27]. Indeed, after long-term administration of pramipexole, NE neurons regained their normal firing rate, due to desensitization of the \( \alpha_2 \)-adrenergic autoreceptors [27]. Importantly, a recent study showed that while the sensitivity of postsynaptic \( \alpha_2 \)-adrenoceptors and 5-HT_1A receptors are not changed after 14 days of administration of pramipexole, there was an enhancement of tonic activation of the 5-HT_1A receptors in hippocampus, and an increase of firing of 5-HT neurons in the DRN [27,96]. This confirms the increase in net 5-HT transmission following long-term administration of pramipexole.

These data revealed that in addition to its effects on the DA system, pramipexole exerts a facilitating action on 5-HT neurotransmission. Drugs with dopaminergic properties may thus act, at least in part, through an action on the 5-HT system. Altogether, these observations strengthen the importance of the interactions between DA, NE, and 5-HT systems.
Nomifensine

Nomifensine, an antidepressant with potent NE and DA reuptake inhibiting properties, was as effective as traditional antidepressants. A comprehensive assessment of the pooled studies provided strong evidence for equal efficacy of nomifensine and imipramine [97,98]. It was removed from the market because of aplastic anemia, unrelated to its reuptake inhibitory actions. Pooled analyses undertaken to explore the generalizability of treatment efficacy provided statistical evidence that more severely depressed patients showed enhanced response to nomifensine relative to placebo.

Animal studies showed that nomifensine markedly decreased the firing rate of NE neurons in the LC after 2 days, with no recovery of the firing rate of these neurons after 14 days [52] (Figure 6), similar to previous results found with the NRI reboxetine and MAOIs [99]. The absence of a recovery in the firing rate of these neurons is likely due to a lack of desensitization of somatodendritic α2-adrenoceptors, which are known to inhibit NE neuronal firing [99]. These α2-adrenoceptors have nevertheless the capacity to desensitize and allow a recovery of firing of NE neurons. This has initially been documented using the SSRI/5-HT2A receptor antagonist, YM992, a drug that enhances NE release [100,101].

Similar to NE neurons, the firing rate of DA neurons in the VTA was significantly decreased with the short-term nomifensine regimen (Figure 4). Unlike NE neurons, however, both the firing rate and burst activity of DA neurons completely recovered to control levels following 14-day of nomifensine administration (Figure 4), due to the desensitization of the somatodendritic D2 autoreceptor, as was reported for a 14-day regimen of the D2 agonist quinpirole [52,95]. Interestingly, nomifensine induced a significant increase in the firing rate of 5-HT neurons after 2 days, which remained significantly elevated after the 14-day regimen. It is well documented that increases in synaptically available NE and DA cause an excitation of DRN 5-HT neurons via α1-adrenoceptors [102] and D2 receptors [53,103], respectively. Although it has been previously reported that acute administration of the NRI reboxetine increases 5-HT firing [42], sustained administration of reboxetine is without effect [99].
Relevance of Norepinephrine–Dopamine Interactions

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Figure 6  Diagrams of NE neurons representing their response and adaptations to the inhibition of the NE and DA transporters with nomifensine or release of DA and NE by bupropion. The spikes on the axons represent the firing activity of NE neurons. The dots around NE neuron represent NE molecules. These neurons have \( \alpha_2 \) autoreceptors that inhibit firing and release when activated by an excess amount of NE. The effects of NE on postsynaptic neurons are mediated by several subtypes of \( \alpha \)- and \( \beta \)-adrenergic receptors. NRI, norepinephrine reuptake inhibitor.

Prolonged administration of desipramine and reboxetine desensitize \( \alpha_2 \)-adrenergic receptors present on 5-HT terminals, leading to an increase in synaptic availability of endogenous 5-HT in the rat hippocampus [104,105]. Nevertheless, as for pramipexole, the increase in 5-HT firing following nomifensine administration indicates that the dopaminergic property of nomifensine likely contributes to increase 5-HT neuronal firing.

The increase in 5-HT neuronal firing following 2 days of nomifensine administration implies a synergistic effect of the dual action of this drug since GBR 12909 and selective NRIs produced no such effect [52,99]. However, the elevation of 5-HT neuronal firing following 2 days of nomifensine administration was abolished by lesion of NE neurons, but not by the administration of the D\(_2\) receptor antagonist paliperidone [52,106,107]. This indicates on the one hand that NE plays a significant role in this increase, and on the other hand, that enhanced DA levels may also play a role but may not be sufficient on its own to induce such an increase. A similar increase in the firing rate of 5-HT neurons was obtained following a 2-day administration of aripiprazole, a D\(_2\) and 5-HT\(_1A\) receptor partial agonist; this increase was reversed by paliperidone, indicating again that it was mediated by D\(_2\) receptors [107]. These data show that nomifensine increases DA, NE and 5-HT transmission. Interestingly, a similar increase in DRN 5-HT neurons firing was obtained following an action through \( \alpha_1 \)-adrenoceptors in the case of nomifensine and through D\(_2\) receptors with aripiprazole.

**Bupropion**

Bupropion is an effective antidepressant when used alone or in combination with SSRIs as an augmentation strategy [108,109]. It has been shown that bupropion has no significant affinity for various types of receptors such as \( \alpha \)- or \( \beta \)-adrenoceptors, 5-HT, DA, or nicotinic receptors [110–112]. Although the mechanism of action of bupropion is not fully understood, DAT inhibition is unlikely because four positron emission tomography (PET) scan studies have reported that clinically effective doses of bupropion produce very low occupancy of dopamine reuptake sites [113–116]. It is unlikely that such low DAT occupancy has an effect on DA transmission since the value obtained is hardly different from baseline [113]. Moreover, a lack of NE reuptake inhibition is indicated by its lack of inhibitory effect on the tyramine pressor response, contrarily to NRIs [117]. In preclinical studies, bupropion was hypothesized to be a NE releaser in LC...
and at the level of NE terminals in DRN [29]. Indeed, administration of subacute bupropion increases firing of 5-HT neurons whereas NNRIs do not. This effect was no longer present in NE-lesioned rats. Finally, it is thought to be mediated through activation of α2-adrenoceptor, which exerts an excitatory action on 5-HT neurons activity [29,118,119]. Administration of bupropion for two days decreased the firing activity of LC neurons (Figure 6) through an overactivation of α2-adrenoceptors, as the selective α2-adrenoceptor antagonist idazoxan reversed this effect [29]. In addition, it was shown that NE neuronal firing recovers after 14 days of bupropion administration [28] (Figure 6), a phenomenon that does not occur with reboxetine, desipramine, or even MAOIs [99,120]. Importantly, the recovery of the firing of LC NE neurons and the desensitization of the autoreceptors after administration of bupropion for 14 days (Figure 7) imply that there could be a sustained increase in NE neurotransmission in brain target areas. Interestingly, the tonic activation of α1-, α2-adrenergic and 5-HT1A receptors by endogenous NE and 5-HT, respectively, was increased following 14 days of bupropion administration [121]. The bupropion regimen that alters NE and 5-HT neuronal firing had no effect on the firing of DA neurons. Previous studies showed that only high intravenous doses of bupropion dose-dependently reduced firing of brainstem dopamine neurons in the rat [30], therefore suggesting that this effect does not constitute a basis for its clinical efficacy in MDD resistant patients. As mentioned above, the use of a dual DA and NRI, nomifensine, was shown to exert a robust antidepressant effect. This strategy has not been exploited since, although triple reuptake inhibitors (5-HT, NE, and DA) 

**Atypical Antipsychotics**

Atypical antipsychotics, despite being D2 receptor antagonists, are even more potent 5-HT2A receptor antagonists [128]. These two properties are believed to underlie their therapeutic action in psychosis, while producing minimal motor side effects. They also have affinities for receptors other than the D2 and the 5-HT2A receptors. Quetiapine apparently differs from other typical and atypical antipsychotic drugs by its antidepressant activity and its proven efficacy in unipolar and bipolar disorders, as well as generalized anxiety disorder [129–131]. Its antidepressant activity could well stem from its α2-adrenoceptor antagonistic activity, which would then be akin to that of mirtazapine, an α2-adrenergic and 5-HT2A receptor antagonist [132,133]. Systemic administration of quetiapine also enhances the extracellular levels of NE and DA in the rat PFC as for mirtazapine [132,134]. Some atypical antipsychotics may thus increase NE and 5-HT transmission by blocking α2-adrenoceptors on LC NE cell body as well as antagonizing α2-adrenoceptors on NE and 5-HT terminals in projection areas [104]. However, not all atypical antipsychotics have activity at α2-adrenoceptors, like olanzapine, which was shown to have a beneficial therapeutic effect in MDD resistant patients to SSRIs [135–137]. This effect is thought to be through action on 5-HT2A receptors located on GABA neurons controlling NE neuronal firing [100]. Indeed, because of their ability to block 5-HT2A receptors, atypical antipsychotics reverse the SSRI-induced inhibition of the firing rate and burst activity of NE neurons, as it was demonstrated for the combination of SSRIs fluoxetine and escitalopram with olanzapine and risperidone, respectively [136–138]. In addition, an important metabolite of quetiapine in humans, norquetiapine, appears to be a blocker of NET (Ki = 58 nM; [139]). Previous studies have shown that blockade of NET together with α2-adrenoceptor antagonism leads to a synergistic effect on extracellular levels of NE [140]. Sustained treatment with NET blockers results in a decrease of NE firing activity without a recovery due to the absence of α2-adrenoceptor desensitization [99]. Antagonism of the α2-adrenoceptors could thus potentiate the effect of NET inhibitors, as will be discussed below when the SNRI venlafaxine is combined with mirtazapine in treatment-resistant patients.

**Antidepressant Combinations Acting on NE and/or DA**

As mentioned above, the use of a dual DA and NRI, nomifensine, was shown to exert a robust antidepressant effect. This strategy has not been exploited since, although triple reuptake inhibitors (5-HT, NE, and DA)
Figure 7 (A) The upper panel represents the integrated histogram of the firing activity of a LC NE neuron (lower panel) that was inhibited by the selective $\alpha_2$-adrenoceptor agonist clonidine and reversed by the selective $\alpha_2$-adrenoceptor receptor antagonist idazoxan. (B) Integrated histogram of the firing activity of a LC NE neuron (lower panel) illustrating the decreased responsiveness to three consecutive intravenous injections of clonidine in a rat treated with bupropion for 14 days, thus indicating a desensitization of $\alpha_2$-autoreceptors.

are currently in development. Most of these agents, however, have a low affinity for DAT. Nevertheless, combinations of antidepressants resulting in at least a dual action on NE and DA have been used with success not only in treatment-resistant depression, but also in drug-naïve patients [141].

For instance, the combination of bupropion and mirtazapine has been shown to nearly double the remission
rate in MDD after 6 weeks of concomitant administration from treatment initiation in a double-blind randomized trial. In the same study, a noradrenergic regimen of venlafaxine combined with mirtazapine produced a 58% remission rate [141]. Similarly, addition of bupropion to the SNRI duloxetine has been reported in an open labeled study to be an effective strategy [142]. Trials examining the antidepressant potential of the addition of the atypical antipsychotics risperidone (an α2-adrenoceptor antagonist) and aripiprazole (a D2 receptor partial agonist) at subtherapeutic regimens for psychosis, therefore not functionally antagonizing D2 receptors, have been shown to be effective with the SNRI venlafaxine [143–145].

**Conclusion**

In summary, agents that act selectively on DA or NE neuronal elements to enhance net transmission of these catecholamines can produce a clear antidepressant action. In addition, these two neuronal systems have important reciprocal anatomical and physiologically important interactions. Some strategies acting on both systems have been shown to be effective, not only in drug naive patients, but also in treatment-resistant depression. Finally, because the DA and NE systems also have reciprocal interactions with the 5-HT system, drugs impacting the DA and NE systems also end up increasing 5-HT transmission (Figure 1, Table 1). On such premises, it can be proposed that combinations of catecholamine actions could help further improve the treatment of MDD.

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**Conflict of Interest**

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