

Review

# Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders

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**Abstract:** Atypical antipsychotic drugs were introduced in the early 1990<sup>th</sup>. Unlike typical antipsychotics, which are effective only against positive symptoms of schizophrenia, atypical antipsychotics show effectiveness against negative and cognitive symptoms as well. Furthermore, they are effective not only in psychotic, but also in affective disorders, by their own or as adjuncts to antidepressant drugs. While typical antipsychotics act, almost exclusively, *via* dopamine-2 (D<sub>2</sub>) receptors, atypical target serotonin-1A/1B/2A/2C (5-HT<sub>1A/1B/2A/2C</sub>),  $\alpha_{1/2}$ -adrenergic, and/or histamine-1 (H<sub>1</sub>) receptors as well. Blocking of 5-HT<sub>1A/1B</sub> autoreceptors, inducing their early desensitization, and/or activation of  $\alpha_1$ -adrenoceptors, allow some atypical drugs to enhance 5-HT transmission. Blocking of 5-HT<sub>2A/2C</sub> and/or  $\alpha_2$ -adrenoceptors enable some atypical antipsychotics to stimulate catecholamine transmission and/or diminish the inhibition of catecholamine neurons induced by some antidepressants. It is possible, that the activation of H<sub>1</sub> and/or blocking of H<sub>3</sub> boost monoamine transmission as well, *via* a mechanism involving stimulation of firing activity of dopamine neurons. The experimental drugs with antipsychotic potential, acting on adenosine and trace amino associated (TAAR) receptors, might be effective in mood disorders as well, because of the ability to modulate the excitability of monoamine-secreting neurons and to potentiate extracellular concentrations of monoamines in the limbic areas of the brain.

**Keywords:** serotonin; norepinephrine; dopamine; histamine; adenosine, trace amines

## 1. Introduction

The first antipsychotic drug, chlorpromazine, belonging to the family of phenothiazines, was serendipitously discovered in 1951. Phenothiazines were the first drugs to show effectiveness to ease the positive symptoms of schizophrenia; however, they were effectiveness against negative and cognitive symptoms and had multiple aversive side effects. Later, another group of typical antipsychotic drugs was discovered: butyrophenones, best known by their representative haloperidol. Haloperidol, introduced into the clinical practice in 1958, remains the most frequently prescribed antipsychotic drug. Butyrophenones have had better effectivity against the positive symptoms of schizophrenia and lesser side effects; however, they were still effectiveness against the negative and cognitive symptoms [1].

The first atypical antipsychotic, clozapine, was introduced into the clinics in 1990. Atypical antipsychotics made a revolution in pharmacotherapy of schizophrenia: they were found to be effective not only against the positive, but also against negative symptoms of schizophrenia. In addition, they have had lesser extrapyramidal motor side effects than phenothiazines and butyrophenones [2, 3]. When atypical antipsychotics entered the clinical practice, it was found out that they improve not only the core symptoms of schizophrenia, but also affective symptoms which are frequently present in schizophrenic patients. Later, the usage of atypical antipsychotic drugs, as monotherapy or as adjuncts to antidepressant and mood stabilizing medicines, became a common and clinical practice also in mood and anxiety disorders [4-6].

In general, atypical antipsychotic drugs as monotherapy are effective in bipolar rather than in unipolar depression [7-9]. Particularly, the clinical effectiveness as a monotherapy in bipolar disorder has been shown for aripiprazole [10, 11], asenapine [12], olanzapine, quetiapine [13], and risperidone [14]. Quetiapine, aripiprazole, olanzapine, and risperidone have also showed effectiveness as monotherapies for generalized anxiety disorder [15].

In unipolar depression, atypical antipsychotic drugs are usually applied in combination with the selective serotonin (5-HT) reuptake inhibitors (SSRIs) or dual 5-HT/norepinephrine reuptake inhibitors (SNRIs) [16-18]. Particularly, creditable effectiveness as adjuncts to antidepressant drugs in treatment-resistant depression was demonstrated for aripiprazole [19], brexpiprazole [20], and risperidone [21].

Interestingly, novel experimental treatment compounds, such as histamine [22-24], adenosine [25-27], and trace-amine receptors-acting agents [28-30], had demonstrated putative antipsychotic, as well as antidepressant efficiency. In these senses, these putative future drugs are similar with the contemporary atypical antipsychotic drugs. In this review, the authors aim to underline the neural mechanisms allowing atypical antipsychotic drugs, currently existing ones, and these under different stages of preclinical or clinical investigation, to be effective in psychotic, as well as in affective disorders.

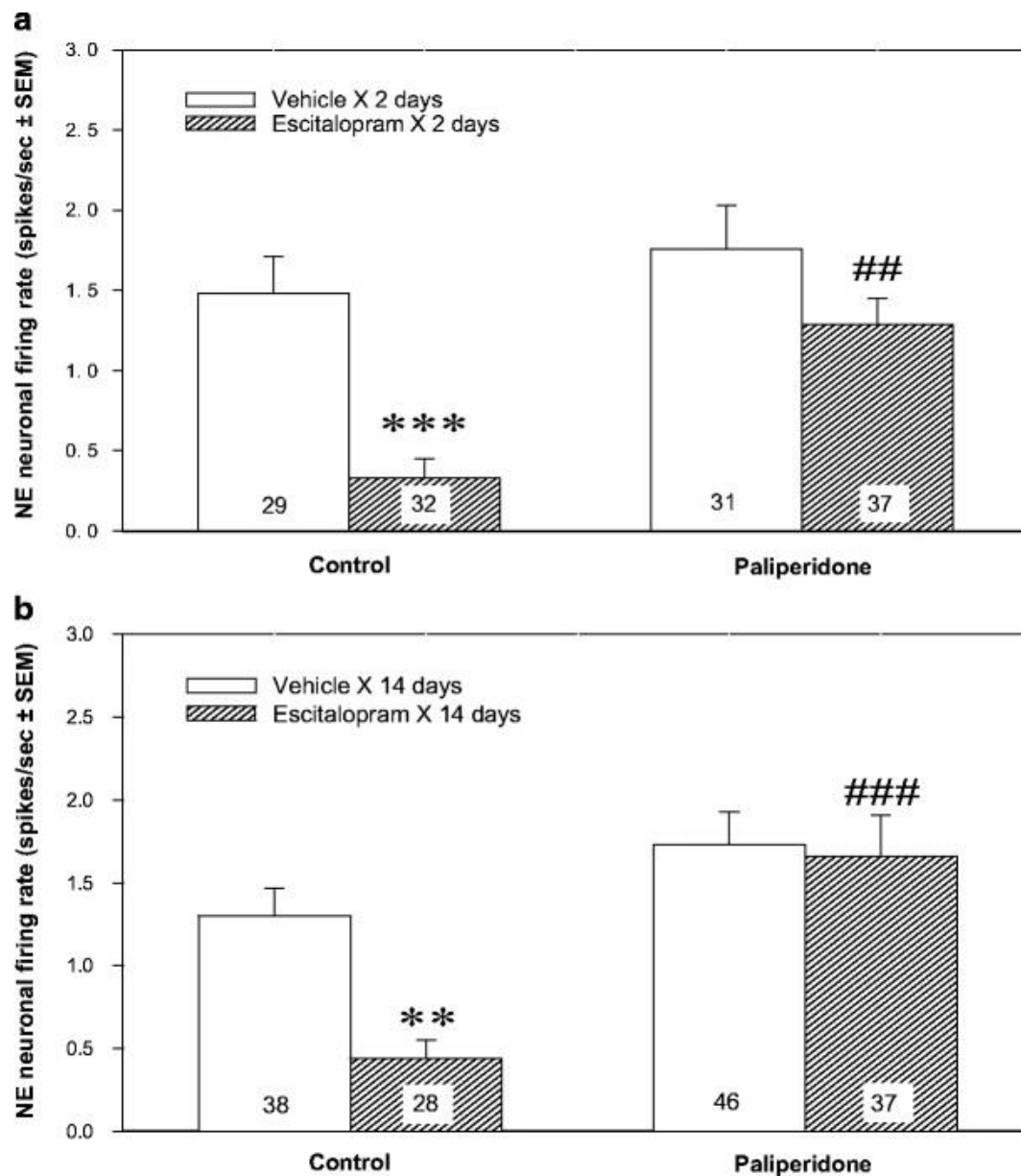
## 2. Mechanism of action of atypical antipsychotics in mood disorders

### 2.1. Serotonergic mechanisms

Classical antipsychotics, such as haloperidol, act almost exclusively on D<sub>2</sub> receptors [31]. As such, they direct interaction with central 5-HT system is limited. It is possibly explaining the lack of efficacy of classical antipsychotic in mood disorders, unless psychotic symptoms are also present, like in psychotic depression or in major manic episode with psychotic features. Unlike typical ones, atypical antipsychotics have affinities to 5-HT<sub>1A</sub>, 5-HT<sub>2A/2C</sub>,  $\alpha_1$ , and/or  $\alpha_2$ -adrenergic receptors, compatible or even higher than these to D<sub>2</sub> receptors [31-33]. Targeting these receptors allow atypical antipsychotics to alter the excitability of 5-HT neurons. This may explain the efficiency of atypical antipsychotics in mood disorders *per se*.

The first direct examinations of the effect of an atypical antipsychotic drugs on the excitability of 5-HT neurons was performed Stark and colleagues [34] by Dremencov and colleagues [35] in 2007. Stark et al reported that aripiprazole reduced the firing activity of 5-HT neurons in the dorsal raphe nucleus (DRN); this aripiprazole-induced inhibition of excitability of 5-HT neurons was reversed by a selective antagonist of 5-HT<sub>1A</sub> receptors, WAY100635, suggesting that the serotonergic effect of aripiprazole is primarily mediated *via* 5-HT<sub>1A</sub> receptors [34]. Similar acute inhibitory effect on 5-HT neurons was reported for risperidone; acute paliperidone, however, did not alter 5-HT neuronal firing activity. Differently from aripiprazole, risperidone-induced inhibition of 5-HT neurons was only partially reversed by WAY100635; the complete reversal was observed after c-administration of WAY100635 and desipramine. Combined 5-HT<sub>1A</sub> serotonergic/ $\alpha_1$ -adrenergic mechanism for the suppressive effect of risperidone on excitability of 5-HT neurons was therefore suggested [35].

Sustained effect of atypical antipsychotic drugs might be different from the acute effect of the same medicines. Thus, sub-chronic and chronic aripiprazole stimulated the firing activity of 5-HT neurons; co-administered with SSRI escitalopram for two days, this drug reverse escitalopram-induced inhibition of 5-HT neurons [36]. Similar stimulatory effect on 5-HT neurons was reported after two and fourteen days of brexpiprazole administration [37]. Sustained asenapine also boosted the excitability of 5-HT neurons, but after two, and not after fourteen days of treatment [38]. Sustained paliperidone did not alter the excitability of 5-HT neurons, while sustained risperidone inhibited it. Even though paliperidone did not alter 5-HT neuronal firing activity by its own, it reversed two-day escitalopram-induced inhibition of 5-HT neurons. Risperidone, co-administered with escitalopram for two days, had similar inhibitory effect of 5-HT neuronal firing activity as the solo administration of each one these drugs (Fig. 1) [35].



**Figure 1.** Serotonergic augmentation of the SSRI escitalopram response by the atypical antipsychotic drug paliperidone. Effect of the paliperidone regimen on the NE neuronal firing rate in the rats administered vehicle or escitalopram. The animals were implanted with minipumps containing vehicle (water) or escitalopram ( $10 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) for 2 (a) or 14 days (b) and received no cotreatment (control) or were co-administered (s.c.) paliperidone ( $1 \text{ mg kg}^{-1} \text{ day}^{-1}$ ). After 2 days, there was a significant effect of the treatment (escitalopram or vehicle,  $F[df 1, 122]=14.76$ ,  $p<0.001$ ) and cotreatment (paliperidone or no cotreatment,  $F[df 1, 122]=8.64$ ,  $p<0.01$ ). After 14 days, there was a significant effect of the treatment  $F[df 1, 165]=5.45$ ,  $p<0.05$ , cotreatment (paliperidone or no cotreatment,  $F[df 1, 165]=17.18$ ,  $p<0.001$ ), and treatment  $\times$  cotreatment interaction ( $F[df 1, 165]=3.98$ ,  $p<0.05$ ). The number of neurons recorded in each group is provided within the histograms. *Triple asterisk*,  $p<0.001$ , *double asterisk*,  $p<0.01$ , in comparison with control animals; *triple number sign*,  $p<0.001$ , *double number sign*,  $p<0.01$ , in comparison with animals administered escitalopram alone. From Dremencov et al., 2007 [35]. Reused with a permission of Springer Nature.

The inhibition of 5-HT reuptake is the pharmacological mechanism of action of the majority of clinically used antidepressant drugs. This mechanism is shared by several tricyclic drugs, such as imipramine and clomipramine, as well as by SSRIs, SNRIs, and the last-generation triple 5-HT, norepinephrine, and dopamine reuptake inhibitors. The highly selective, last generation SSRIs, as citalopram and escitalopram, elevate extracellular 5-HT levels within minutes after their intake [39,

40]. The onset of their clinical therapeutic effect is not however observed earlier than after two weeks of sustained drug administration. The inhibition of 5-HT neuronal firing activity is one of the mechanisms putatively responsible for the delayed response to antidepressant drugs. Thus, SSRIs, SNRIs, and triple 5-HT, norepinephrine and dopamine reuptake inhibitors increase at first extracellular 5-HT levels in the raphe nuclei, where 5-HT transporters (SERTs) are densely expressed. This leads to the activation of somatodendritic 5-HT<sub>1A</sub> autoreceptors and to the inhibition of firing activity of 5-HT neurons [39, 41-47]. As a result, the net 5-HT transmission, especially at the nerve terminals level, remains unchanged. Only after at least two weeks of treatment, when somatodendritic 5-HT<sub>1A</sub> autoreceptors start to desensitize and 5-HT neuronal firing activity recovers to basal levels, the net 5-HT transmission starts to be boosted by SSRIs and their therapeutic behavior effect starts to be observed [48-51].

The therapeutic of some atypical antipsychotics, such as aripiprazole, brexpiprazole, and asenapine, as monotherapy in mood and anxiety disorders, might be therefore explained, at least in part, by the ability of these drugs to stimulate the firing activity of 5-HT neurons. The beneficial mood effect of quetiapine might be explained by the ability of this drug to increase the sensitivity of postsynaptic hippocampal 5-HT<sub>1A</sub> receptors to 5-HT [52]. The beneficial effect of certain atypical antipsychotic drugs, such as aripiprazole and paliperidone, as adjuncts to SSRIs in treatment-resistant depression, might be explained by the ability of these drugs to reverse the SSRI-induced inhibition of 5-HT neuronal firing activity, especially at early stages of SSRI treatment. The mechanisms allowing atypical antipsychotics to boost 5-HT excitability or to reverse SSRI-induced inhibition of 5-HT neurons is not yet completely understood. This mechanism is perhaps involving a rapid sensitization of 5-HT<sub>1A</sub> autoreceptors and/or sensitization of  $\alpha_1$ -adrenergic receptors in the DRN [4, 5].

## 2.2. Noradrenergic mechanisms

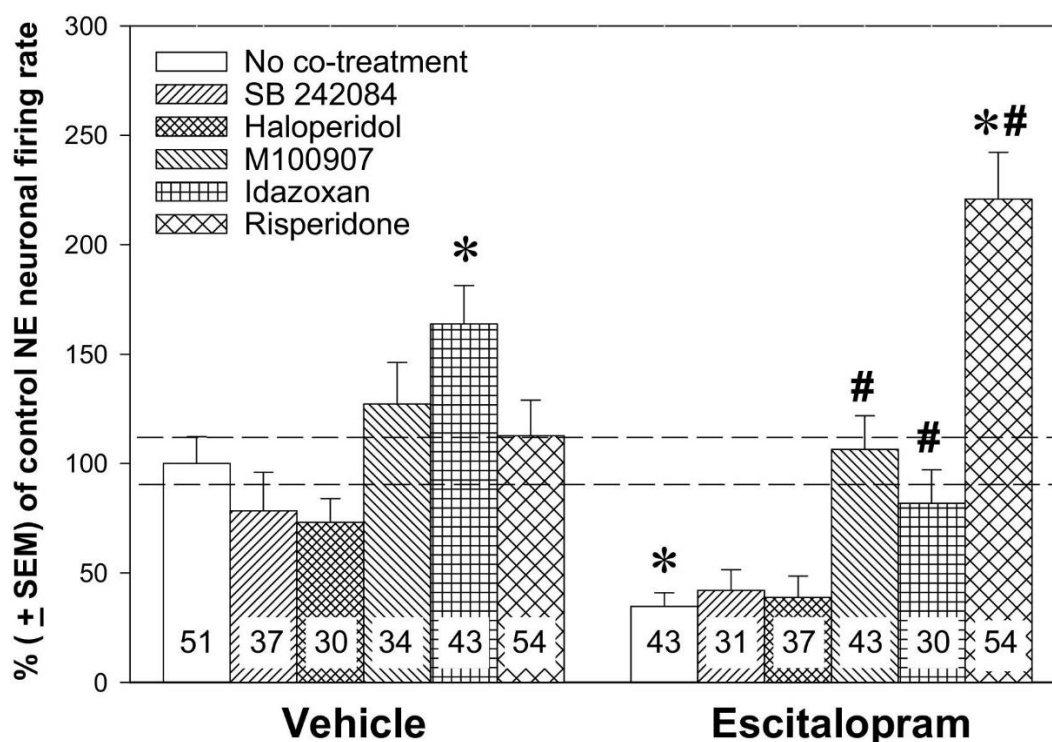
Norepinephrine is a catecholamine acting as hormone and as a central and peripheral neurotransmitter. In the CNS, norepinephrine responsible for alertness, concentration, and energy [53]. Since fatigue and concentration difficulty are frequent symptoms of depression [54], norepinephrine is likely to be involved in pathophysiology of this disorder. On the other side, some antidepressant drugs, such as SSRIs, have a suppressing effect of norepinephrine transmission. Thus, citalopram and escitalopram both inhibit the excitability of norepinephrine neurons of rat locus coeruleus (LC), escitalopram after two, and citalopram after fourteen days of treatment [35, 55]. The faster effect of escitalopram, comparing to citalopram, on the excitability of LC norepinephrine neurons is putatively explained by its higher selectivity and efficacy as 5-HT reuptake inhibitor [39, 40]. Unlike SSRI-induced inhibition of 5-HT neurons of the DRN, which disappears after sustained (two weeks or more) SSRIs administration due to desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors, SSRI-induced inhibition of norepinephrine neurons of the LC remains in force even after prolonged treatment [35, 36, 55-57]. It was reported that the SSRI-induced inhibition of norepinephrine neuronal firing activity is mediated, at least in part, *via* 5-HT<sub>2A</sub> receptors [58, 59].

It was reported that the typical antipsychotic drug haloperidol did not alter the excitability of norepinephrine neurons of the LC by its own and did not alter the SSRI escitalopram-induced inhibition of firing activity of LC norepinephrine neurons [55]. An atypical antipsychotic drug olanzapine, however, stimulated the excitability of norepinephrine neurons of the LC after an acute administration [60]. Increased activity of norepinephrine neurons was found after sub-chronic and chronic aripiprazole [36], quetiapine [52], and brexpiprazole; brexpiprazole also increased sensitivity of hippocampal  $\alpha_2$ -adrenoceptors to norepinephrine [37]. Asenapine boosted norepinephrine neuronal excitability after fourteen, but not after two days of treatment [38]. On the other hand, acute, sub-chronic, and chronic risperidone and paliperidone did not alter the norepinephrine neuronal firing activity in the LC [35, 55, 61].

In 2007, Dremencov and colleagues performed a pharmacological dissection of the effect of risperidone, alone or in combination with escitalopram, on the excitability of norepinephrine neurons of the LC [55]. Since risperidone is a potent 5-HT<sub>2C</sub>, D<sub>2</sub>, 5-HT<sub>2A</sub>, and  $\alpha_2$ -adrenoceptor antagonist,



selective antagonists of these receptors (SB 242084, haloperidol, M100907, and idazoxan, respectively) were administered, alone or in combination with escitalopram, to assess whether their effect is similar to this of risperidone (Fig. 2):



**Figure 2.** Noradrenergic augmentation of the SSRI escitalopram response by the atypical antipsychotic drug paliperidone and its pharmacological dissection. The animals were implanted with minipumps containing water or escitalopram (10 mg/kg/day) for 2 days and received no co-treatment (control animals) or were co-administered (SC) the atypical antipsychotic risperidone (1 mg/kg/day), the 5-HT<sub>2C</sub> antagonist SB 242084 (.5 mg/kg/day), the D<sub>2</sub> antagonist haloperidol (.1 mg/kg/day), the 5-HT<sub>2A</sub> antagonist M100907 (.5 mg/kg/day), or the  $\alpha_2$ -adrenergic antagonist idazoxan (1 mg/kg/day) for 2 days. Two-way ANOVA showed a significant effect of the treatment [escitalopram or vehicle,  $F(1,486)=5.41$ ,  $p < .05$ ], of the co-treatment [risperidone, SB 242084, M100907, haloperidol, idazoxan, and no co-treatment,  $F(5,486) = 17.18$ ,  $p < .001$ ], and treatment x co-treatment interaction [ $F(5,486) = 11.07$ ,  $p < .001$ ]. \* $p < .01$ , in comparison with control animals; # $p < .05$ , in comparison with animals administered escitalopram alone, using a Bonferroni post hoc test. The number of neurons recorded in each group is provided within the histograms. SC, subcutaneous; 5-HT<sub>2C</sub>, serotonin 2C receptor; D<sub>2</sub>, dopamine-2; 5-HT<sub>2A</sub>, serotonin 2A receptor; ANOVA, analysis of variance. From Dremencov et al., 2007 [55]. Reused with a permission of Elsevier.

As it was already stated above, risperidone by its own did not alter norepinephrine firing activity; neither did SB 242084, haloperidol, or M100907. Only idazoxan increased the firing activity of 5-HT neurons. Escitalopram, as it was already stated above, robustly suppressed the excitability of norepinephrine neurons of the LC. SB 242084 or haloperidol did not alter the escitalopram-induced inhibition of norepinephrine neurons. M100907 and idazoxan successfully reversed the inhibition of norepinephrine neurons induced by escitalopram. Risperidone not only reversed the escitalopram-induced excitability of norepinephrine neurons, but also boosted the firing activity of norepinephrine neurons above the values recorded in control rats. Paliperidone [35], aripiprazole [36], and quetiapine [52] also reversed the SSRI-induced inhibition of norepinephrine neurons; however, these drugs did not boost the firing of norepinephrine neurons to the values higher than in control animals.

Summarizing, beneficial mood effect of some atypical antipsychotics, such as aripiprazole, quetiapine, and brexpiprazole in mood disorders might be mediated via their ability to stimulate, might be mediated, at least partially, *via* their ability to enhance the excitability of norepinephrine

neurons, *via* an  $\alpha_2$ -adrenoceptor-mediated mechanism. Beneficial effect of antipsychotic drugs as adjuncts to SSRIs might be explained, at least in part, by their ability to reverse the SSRI-induced inhibition of norepinephrine neuronal firing activity [4, 62, 63].

### 2.3. Dopaminergic mechanisms

Dopamine is a brain catecholamine transmitter primarily responsible for reward and motivation [53]. Since anhedonia is a primary symptom of depression [54], dopamine is likely to be involved in pathophysiology of this illness. On the other hand, at least some SSRIs have an inhibitory effect on dopamine transmission (VTA). The inhibitory effect of sustained SSRIs escitalopram and citalopram was demonstrated by Dremencov and colleagues; this effect was mediated, at least in part, *via* 5-HT<sub>2C</sub> receptors [64]. Similarly to the SSRI-induced inhibition of norepinephrine neurons and unlike SSRI-induced suppression of 5-HT neurons, the inhibition of dopamine neurons by SSRIs remains in force even after prolonged SSRI administration [36, 64, 65]. It is thus possible that the lack of adequate response to SSRIs, at least in some patients, can be mediated, at least in part, *via* the 5-HT<sub>2C</sub> receptor-mediated inhibition of firing activity of 5-HT neurons.

It was reported that chronic administration of asenapine increased the density of spontaneously active dopamine neurons in the VTA, while firing parameters remained unchanged. Asenapine, administered for two days, partially reversed the inhibition of dopamine neuronal firing activity, induced by apomorphine, an agonist of D<sub>2</sub> receptors. This effect was lost after chronic asenapine administration, suggesting adaptive changes leading to D<sub>2</sub> receptor sensitization [38]. Aripiprazole, however, did not alter the excitability of dopamine neurons by its own. Nevertheless, when it was co-administered with escitalopram for two of fourteen days, aripiprazole reversed escitalopram-induced inhibition of excitability of dopamine neurons of the VTA [36]. It can be thus summarized that some atypical antipsychotics, such as asenapine, are beneficial in mood disorders because of their ability to stimulate mesolimbic dopamine transmission, by increasing the density of spontaneously active dopamine neurons in the VTA. This beneficial mechanism is putatively involving desensitization of D<sub>2</sub> autoreceptors. Other atypical antipsychotic drugs, such as aripiprazole, are beneficial as adjuncts to SSRIs because of their ability to reverse SSRI-induced inhibition of dopamine neuronal firing activity, *via* a mechanism putatively involving 5-HT<sub>2C</sub> receptors activity [4, 62, 63].

### 2.4. Histaminergic mechanisms

Some atypical antipsychotics, such as clozapine, olanzapine, and quetiapine, are binding to histamine-1 (H<sub>1</sub>) receptors with the affinity compatible to this for D<sub>2</sub>, 5-HT<sub>2A/2C</sub>, and  $\alpha_2$ -adrenoceptors [31-33]. Interaction of CNS drugs with histamine receptors has been traditionally seen as responsible for the side effect of these drugs on the immune system rather than for their therapeutic potential. However, since central histamine is involved sleep, cognition, memory, and emotions [66, 67], the therapeutic potential of histamine receptors started to attract attention [68].

*In vivo* interaction between histamine and other monoamines (5-HT, norepinephrine, and dopamine) was demonstrate in electrophysiological and microdialysis studies by Flik and colleagues. It was found that increase in brain histamine levels, induced by a partial agonist of histamine-3/4 (H<sub>3/4</sub>) receptors thioperamide [69], led to the subsequent elevation of extracellular 5-HT, norepinephrine, and dopamine concentrations in prefrontal cortex (PFC) and hypothalamus [70].

Even though thioperamide increased brain dopamine, as well as 5-HT and norepinephrine concentrations, it stimulated the firing activity of dopamine, but not 5-HT and norepinephrine neurons. Immapip, an antagonist of H<sub>3</sub> receptors, inhibited dopamine (but not 5-HT and norepinephrine) neurons by its own and reversed thioperamide-induced stimulation of dopamine neuronal firing activity. The stimulatory effect of thioperamide on the excitability of dopamine neurons was mimicked by a direct iontophoretic administration of histamine into the VTA. It was thus suggested that thioperamide increase extracellular histamine levels in certain brain areas, including the VTA, and it leads to the stimulation of dopamine-secreting neurons therein, *via* a mechanism potentially involving histamine-1 (H<sub>1</sub>) receptors [70]. It is therefore possible that the

antagonists of H<sub>3</sub> and/or agonists of H<sub>1</sub> receptors might be beneficial in mood and psychotic disorders, by their own and/or as adjunct to antipsychotic and/or antidepressant drugs, because of their ability to stimulate brain monoamine transmission.

#### 2.4. Purinergic mechanisms

So far, receptors to purines, such as adenosine-2A (A<sub>2A</sub>) receptors, are not targeted by the contemporary antipsychotic drugs, either typical or atypical. However, there is evidence for the involvement of these receptors in both psychotic and affective disorders and their potential role as a target for next-generation CNS medicines. An antipsychotic effect of an agonist of A<sub>2A</sub> receptors, CGS 21680, in laboratory primates was demonstrated by Andersen and colleagues in 2002 [71]. This antipsychotic-like effect of CGS 21680 was explained by its ability to attenuate the affinity postsynaptic D<sub>2</sub> receptors in the striatum to dopamine [72-74]. It was latterly reported that A<sub>2A</sub> and D<sub>2</sub> receptors are interacting on the molecular level: these two receptors are capable to form heterodimers. Furthermore, A<sub>2A</sub>-D<sub>2</sub> heterodimers have different signal transduction mechanism (G $\alpha$ <sub>q/z</sub> protein-mediated) than A<sub>2A</sub> (G $\alpha$ <sub>s</sub> protein-mediated) or D<sub>2</sub> receptors (G $\alpha$ <sub>i/o</sub> protein-mediated) [75].

*In vivo* microdialysis and electrophysiological examination of the effect of an agonist (CGS 216820) and an antagonist (ZM 241385) of A<sub>2A</sub> receptors, alone or in combination with the classic antipsychotic drug haloperidol, on the excitability of dopamine and norepinephrine neurons and on concentrations of catecholamines in the PFC and nucleus accumbens (NAcc) was performed by Dremencov and colleagues in 2017 [76]. It was found that an antagonist of A<sub>2A</sub> receptors, CGS 216820, inhibited the firing activity of norepinephrine neurons of the LC and dopamine neurons of the VTA, and an antagonist A<sub>2A</sub> receptors, ZM 241385, reversed CGS 216820-induced inhibition of norepinephrine and dopamine neurons. ZM 241385 did not alter extracellular levels of catecholamines but its own, but it potentiated the effect of haloperidol on NAcc dopamine and PFC norepinephrine. It is thus possible that the ligands A<sub>2A</sub> receptors might be beneficial in affective and psychotic disorders, by their own and/or as adjunct to antipsychotic and/or antidepressant drugs, because of their ability to modulate central catecholamine transmission.

#### 2.4. Trace aminergic mechanisms

Trace amines are biological molecules which are present in the mammal brain in trace concentrations. The trace amines include phenethylamines (phenethylamine, n-methylphenethylamine, phenylethanolamine, m- and p-tyramine, 3-methoxytyramine, n-methyltyramine, m- and p-octopamine, and synephrine), thyronamines (3-iodothyronamine), and tryptamines (tryptamine). Trace amines are closely related to the "classical" monoamines from the structural and metabolic points of view [77].

Because of their unneglectable concentrations, trace amines were considered lacking any important biological function. However, the discovery of trace amine acid receptors (TAARs) in 2001 indicated that trace amines are important signaling molecules acting as brain neurotransmitters [78]. Eight TAARs are so far identified: TAAR1, TAAR2, TAAR5, TAAR6, and TAAR8. All TAARs are GPCRs. TAAR1 is believed to be G<sub>s</sub>, TAAR5-G<sub>s</sub> and/or G<sub>q</sub>, and TAAR8-G<sub>i</sub>-coupled [79].

TAAR1 receptors are of special interest as a target for the future antidepressant and antipsychotic drugs. Three lines of evidence support this hypothesis. First, TAAR1 receptors are densely expressed in the brain, and particularly in the DRN and VTA [80]. Secondly, some TAAR1 ligands had shown antidepressant- and antipsychotic like effect in rodents and in primates. Thus, the full agonist RO5256390 decreases rats' immobility time during the FST, and both RO5256390 and the partial TAAR1 agonist RO5263397 improve monkeys' differential reinforcement for low-rate (DRL) scores [28]. Third, TAAR1 ligands were shown to modulate monoamine neurotransmission. RO5256390 [28] and another agonist of TAAR1, RO5166017 [81] were shown to inhibit *ex vivo* excitability of 5-HT and dopamine neurons in brain slices. Consistently, knockout mice lacking TAAR1 showed decreased *ex vivo* excitability of 5-HT and dopamine neurons [80]. The same study

showed, using *in vivo* microdialysis, that TAAR1-knockout mice have increased concentrations of catecholamines in the NAcc and 5-HT levels in the PFC. Finally, inhibitory effect of the acute RO5256390 on 5-HT neurons of the DRN and dopamine neurons of the VTA, and reserving effect of RO5166017 on RO5256390-induced inhibition of 5-HT and dopamine neuronal firing activity were shown in *in vivo* conditions [82]. The antidepressant-like behavioral effects of RO5256390 and RO5263397 in laboratory animals, observed in previous studies [28], might be explained, at least in part, by the ability of these compounds to modulate the excitability of 5-HT and dopamine neurons.

### 3. Summary

The experimental findings on the effect of typical and atypical antipsychotic drugs, administered alone or in combination with the SSRIs, are summarized in the Table 1. The stimulatory effect some atypical drugs of 5-HT neuronal firing activity, such as asenapine, aripiprazole, and brexpiprazole, and their diminishing effect on sub-chronic-SSRI-induced inhibition of 5-HT neurons, is putatively mediated via the blockade of 5-HT<sub>1A</sub> autoreceptors and induction of their rapid desensitization. The diminishing effect of paliperidone sub-chronic-SSRI-induced inhibition of 5-HT neurons might be mediated via 5-HT<sub>1A/1B</sub> and/or  $\alpha_1$ -adrenoceptor-mediated mechanisms. The diminishing effects of atypical antipsychotic drugs on SSRI-induced inhibition of norepinephrine and dopamine neurons are 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub>-mediated, respectively. The  $\alpha_2$ -adrenoceptor antagonistic property of some atypical drugs, such as olanzapine and risperidone, contribute to their norepinephrine-mediated mechanism of action as well.

### 4. Conclusion

Atypical, but not typical antipsychotic drugs enhance 5-HT, norepinephrine and/or dopamine transmission by their own and/or diminish the inhibition of firing activity of monoamine-secreting neurons, induced by some antidepressant drugs. These lines of evidence are well correlating with the clinical observations, suggesting that atypical, but not typical antipsychotic drugs are effective against negative and cognitive symptoms of schizophrenia, as well as against affective symptoms in mood and anxiety disorders. It is thus possible that similar pathophysiological mechanisms underline negative symptoms of schizophrenia and mood disorders, and the effective treatment of both requires simultaneous boosting of 5-HT, norepinephrine, and dopamine transmission.



Drug	Neurophysiological effect	
	By its own	In combination with SSRIs
<i>Currently used atypical antipsychotic drugs</i>		
Aripiprazole	5-HT neurons↓ (acute) 5-HT neurons↑ (sub-chronic, chronic) NE neurons↑ (sub-chronic, chronic)	SSRI-induced 5-HT inhibition (sub-chronic) ↓ SSRI-induced NE inhibition (sub-chronic, chronic) ↓ SSRI-induced DA inhibition (sub-chronic, chronic) ↓
Asenapine	5-HT neurons↑ (sub-chronic) NE neurons↑ (chronic) DA neurons↑ (chronic)*	
Brexipiprazole	5-HT neurons↑ (sub-chronic, chronic) NE neurons↑ (sub-chronic, chronic)	
Olanzapine	NE neurons↑ (acute)	
Paliperidone		SSRI-induced 5-HT inhibition (sub-chronic) ↓ SSRI-induced NE inhibition (sub-chronic, chronic) ↓
Risperidone	5-HT neurons↓ (acute, sub-chronic, chronic)	SSRI-induced NE inhibition (sub-chronic, chronic) ↓**
Quetiapine	NE neurons↑ (sub-chronic, chronic)	SSRI-induced NE inhibition (sub-chronic, chronic) ↓
<i>Putative novel atypical antipsychotic drugs</i>		
Thiopramide (H <sub>3/4</sub> partial agonist)	DA neurons↑ (acute)	
ZM 241385 (A <sub>2A</sub> antagonist)	DA neurons↑ (acute)	
RO5263397 (TAAR1 partial agonist)	5-HT neurons↑ (acute) DA neurons↑ (acute)	

**Figure 2.** Noradrenergic augmentation of the SSRI escitalopram response by the atypical antipsychotic drug paliperidone and its pharmacological dissection.

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## Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
CNS	Central nervous system
LC	Locus coeruleus
NAcc	Nucleus accumbens
PFC	Prefrontal cortex
SNRIs	Selective serotonin reuptake inhibitor
SSRIs	Dual serotonin and norepinephrine reuptake inhibitor
TAAR	Trace amine associated receptor
VTA	Ventral tegmental area

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