Partial Dopamine D_2/Serotonin 5-HT_{1A} Receptor Agonists as New Therapeutic Agents

Adeline Etievant[#], Cécile Bétry[#], and Nasser Haddjeri*[,1]

Laboratory of Neuropharmacology, Faculty of Pharmacy, University Lyon I, EAC CNRS 5006, 8 Avenue Rockefeller 69373 LYON Cedex 08 France

Abstract: The therapeutic efficacy of current antipsychotic or antidepressant agents still present important drawbacks such as delayed onset of action and a high percentage of non-responders. Despite significant advancements in the development of new drugs with more acceptable side-effect profiles, patients with schizophrenia or major depression experience substantial disability and burden of disease. The present review discusses the usefulness of partial dopamine D_2/serotonin 5-HT_{1A} receptors agonists in the treatment of schizophrenia, major depression and bipolar disorder as well as in Parkinson's disease. Partial agonists can behave as modulators since their intrinsic activity or efficacy of a partial agonist depends on the target receptor population and the local concentrations of the natural neurotransmitter. Thus, these drugs may restore adequate neurotransmission while inducing less side effects. In schizophrenia, partial DA D_2/5-HT_{1A} receptor agonists (like aripiprazole or bifeprunox), by stabilizing DA system via a preferential reduction of phasic DA release, reduce side effects i.e. extrapyramidal symptoms and improve cognition by acting on 5-HT_{1A} receptors. Aripiprazole appears also as a promising agent for the treatment of depression since it potentiates the effect of SSRIs in resistant treatment depression. Concerning bipolar disorders aripiprazole may have only a benefit effect in the treatment of manic episodes. Conversely, treatment of Parkinson's disease with partial DA D_2/5-HT_{1A} receptor agonists remains still experimental. However several studies suggest that these drugs decrease usually observed side effects (dyskinesia, psychotic-like symptoms) in Parkinson's disease treatment. Hence, these relatively recent researches provide an exciting future in the discovery of novel stabilizators agents for the management of the latter diseases.

Keywords: Partial agonists, dopamine, serotonin, pschiatric disorders.

INTRODUCTION

Current treatments of neuropsychiatric diseases like schizophrenia and major depression are problematic and unsatisfactory and novel approaches in treating these diseases are desirable. Alterations in monoamine neurotransmission, particularly dopamine (DA) and serotonin (5-hydroxytryptamine, or 5-HT), have been implicated in these diseases. Partial dopamine 2 (D_2)/5-HT_{1A} receptor agonists behave as neuronal modulators or stabilizators and seem to restore adequate neurotransmission without inducing severe side effects. In schizophrenia and affective disorders, aripiprazole is the only commercially representative of this pharmacological class. This review will focus on the recent findings of these new drugs, presently under clinical and preclinical investigations, in relation to treatment of schizophrenia, major depression, bipolar disorders and Parkinson's disease.

Regulation of brain DA and 5-HT transmission

DA System

Five subtypes of DA receptors have been described. According to their pharmacological characteristics and their association with G-coupled proteins and adenylyl cyclase, they are grouped in two main family subtypes: D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3 and D_4). Four DA pathways have been characterized: the mesolimbic, the mesocortical, the nigrostriatal and the tubero-infundibular pathways.

The mesolimbic dopaminergic pathway contains A10 dopaminergic neurons located within the ventral tegmental area (VTA); their associated efferent targets in the ventral striatum including nucleus accumbens (NAcc) and limbic structures (e.g. amygdala and hippocampus). The mesolimbic dopaminergic pathway is involved in emotional and motivational processing [1]. Dysregulation of DA may is currently associated to drug abuse [2]. Moreover, paranoia and psychosis induced by long-term stimulant abuse are similar to schizophrenia symptoms. In schizophrenia, the hyperactivation of the mesolimbic dopaminergic pathway seems to lead to positive symptoms like hallucinations [3].

The mesocortical dopaminergic pathway consists of the A10 dopaminergic neurons and their associated efferent targets in the prefrontal cortex. Contrary to the mesolimbic pathway, the mesocortical pathway is hypoactive in schizophrenia which can be responsible for cognitive and negative symptoms [4].

The nigrostriatal dopaminergic pathway consists of the substancia nigra pars compacta (SNc-A9) and their associated efferent targets in the dorsal striatum. It contains the

*Address correspondence to this author at the EAC CNRS 5006, Laboratory of Neuropharmacology, Faculty of Pharmacy, University of Claude Bernard, 8, Avenue Rockfeller, Lyon 69373, France; Tél: 33-6-26-68-82-15; Fax: 33-4-78-77-72-09; E-mail: nhaddj@sante.univ-lyon1.fr
[#]Both authors contributed equally to this review.

1876-5238/10

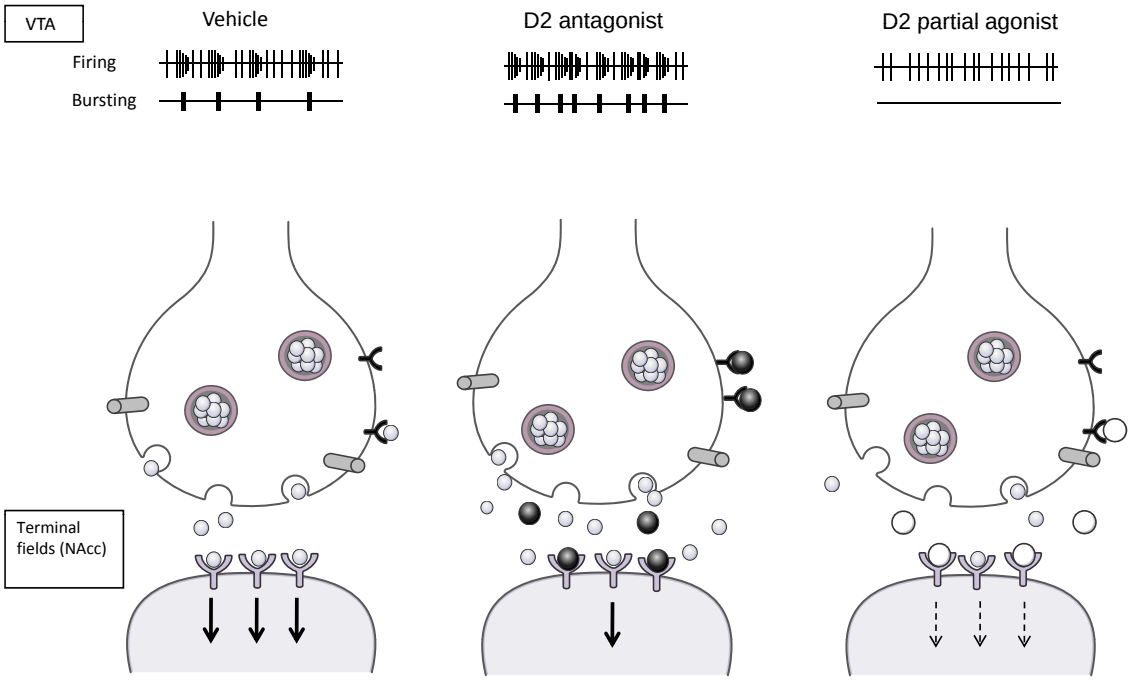

Fig. (1). Hypothetic model of the mechanism of action of partial D_2 /5-HT_{1A} agonists. D_2 receptors are localized on cell body of DA neurons and on their axonal terminations e.g. in the nucleus accumbens (Nacc). DA (small white circles) is released from the axon and activates pre and post-synaptic D_2 (grey Y-shaped) receptors altering the activity of the postsynaptic neurons. Moreover, DA release can be negatively modulated by presynaptic D_2 receptors (dark Y-shaped) and by dopamine transporters (grey small tubes).

At the cell body level, the blockade of D_2 receptors by typical or atypical antipsychotics (big black circles) often increases the neuronal activity of DA neurons. At the postsynaptic level, these compounds reduce the DA signal by blocking D_2 receptors as well as reducing feedback inhibition on release.

At the cell body level, the activation of D_2 receptors by partial agonists (big white circles) moderately decrease the DA neuronal firing with a preferential effect on phasic activity (i.e. on bursting) compared to tonic activity (i.e. on firing). Partial DA agonists present high affinity for the DA receptors and a relatively low efficacy. Consequently, their effect is dependent on the intrinsic concentration of DA and on the receptor occupancy. In the VTA and SNc, where endogenous DA is relatively low, partial DA agonists bind largely D_2 autoreceptors and act as agonists (decreasing firing). Differently, in the Nacc for instance, level of DA is relatively high, partial D_2 agonists act as antagonists.

majority of brain DA[1]. The SNc-A9 pathway is involved in motor learning and control. Degeneration of this pathway leads to Parkinson's disease. In addition, blockade of this pathway is associated with movement disorders like extrapyramidal symptoms (EPS) and dyskinesia.

The tubero-infundibular DA pathway consists of DA neurons that project from the periventricular and arcuate nuclei of the hypothalamus to the intermediate lobe of the pituitary. Secretion of prolactine from the lactotroph cells in the pituitary is under the control of DA released by the tuberoinfundibular pathway. Consequently, blockade of DA receptors induces hyperprolactinemia [5].

DA Partial Agonist

While an agonist mimics the action of a natural neurotransmitter, a partial agonist induces a reduced signaling response compared to the maximum achievable response by a full agonist. The intrinsic activity or efficacy of a partial agonist depends on the sensitivity and responsiveness of the receptors, thus partial agonists can behave as an agonist or antagonist, depending on the target receptor population and the local concentration of the natural neurotransmitter [6]. For example, a partial agonist may act as a DA receptor agonist in the SNc and VTA, where the D_2 receptors are somatodendritic autoreceptors and the amount of endogenous DA is relatively low, but as an antagonist at the post-synaptic D_2 receptors in the striatum, where the amount of endogenous DA is high [7]. The stimulation of DA autoreceptors suppresses neural firing, whereas the stimulation of terminal receptors inhibits the release of DA [7]. In the VTA, the main receptors involved in mediating local effects of DA are D_2 autoreceptors [8]. Nevertheless, it has also been shown that D_1 and possibly D_3 receptors may play a role in control of DA firing and release [9-11].

In vivo, DA neurons have two types of cellular activity: a tonic activity corresponding to firing and a phasic activity corresponding to bursting. Indeed, they exhibit tonic irregular single spike firing interrupted by bursts of spikes often with decreasing spike amplitude followed by brief silences [12]. It has been also shown that the mean firing rate and the bursting pattern of DA neurons can be modulated independently [13]. A state-dependent shift in discharge pattern might be crucial since burst firing of DA neurons was shown to result in a much larger synaptic DA accumulation than single spike firing [13,14].

5-*HT System*

The 5-HT cell bodies in the brain are located in the brainstem near or on the midline. There is nine 5-HT nuclei in the brainstem [B1-B9, 15] that can be divided in the superior

group and the inferior group [see 16]. The superior group consists of the caudal linear nucleus (B8), median raphe nucleus (MRN; B8 and B5), dorsal raphe nucleus (DRN: divided in medial, lateral and caudal components; B7 and B6), and the lateral B9 nucleus located dorsal to the medial lemniscus. The inferior group consists of the nuclei raphe obscursus (B2), raphe pallidus (B1 and B4), raphe magnus (B3) in the ventral lateral medulla (B1/B3) and in the area postrema. The DRN contains about 50-60% of 5-HT neurons in both rat and human CNS, whereas the MRN contains about 5% [17-19]. In the DRN, about 70% of the cells are 5-HT neurons. Non-5-HT cells found in the DRN include peptidergic neurons such as Substance P [20] and non-peptidergic neurons such as DA [21] or GABA [22]. Efferent 5-HT projections to the forebrain originate mainly from the superior group of raphe nuclei. In the rat, the largest pathway is the medial forebrain bundle, which contains fibers from the MRN and DRN to a wide range of target areas in the forebrain. Based on radioligand binding properties, signal transduction and deduced amino acid sequences, 5-HT receptors are categorized as follows : 5-$HT_{1A,B,D,E,F}$ subtypes, which are negatively coupled to adenylyl cyclase; 5-$HT_{2A,B,C}$ subtypes, which are positively coupled to phospholipase C; 5-HT_3 receptor equivalent to the M receptor of Gaddum and Picarelli [23], which incorporates a ligand-gated ion channel; and the 5-$HT_{4,5,6,7}$ subtypes, which are positively coupled to adenylyl cyclase [24].

5-HT_{1A} receptors are located presynaptically on 5-HT neurons in the raphe nuclei and on post-synaptic neurons in the brain and spinal cord. 5-HT_{1A} receptors located on the cell body exert negative feedback on firing activity: when activated by an excess amount of 5-HT, or by an exogenous agonist, they hyperpolarize 5-HT neurons, thereby decrease the firing activity [25] consequently decreasing 5-HT release in projecting structures [26]. The postsynaptic 5-HT_{1A} receptors, which are particularly abundant in limbic structures, commonly exert an inhibitory function on neuronal activity.

PARTIAL DOPAMINE D_2/SEROTONIN 5-HT_{1A} RECEPTOR AGONISTS AND SCHIZOPHRENIA

Schizophrenia is one of the most socially relevant psychiatric disorders, affecting one percent of the population. This disorder is characterized by positive (e.g. delusions, hallucinations, agitation) and negative symptoms (e.g. anhedonia, a-sociality, apathy) [27]. Furthermore, cognitive impairments generally associated with this disorder include deficits in attention, working memory, declarative memory and motor performance [28]. While the pathophysiology of schizophrenia is not fully understood, there is a large body of evidence that schizophrenia is associated with abnormalities in monoamines brain neurotransmission.

Based on pharmacological evidence, deficits in DA neurotransmission have been suggested as the mechanism underlying schizophrenia, leading to the "DA hypothesis of schizophrenia" [29]. More recent imaging techniques such as positron emission tomography (PET) have provided corroborating evidence for this hypothesis [30].

Therapeutic Agents for Schizophrenia

All antipsychotics reduce DA neurotransmission by blocking DA receptors [4], and are commonly divided in two generations. The first-generation "typical" antipsychotics reduce DA neurotransmission by blocking DA receptors, predominantly the D_2 subtypes. While they reduce positive symptoms, they have the drawback of causing important side effects [29]. For example, they can induce extrapyramidal symptoms (EPS) similar to Parkinsonism syndrome. EPS are directly related to D_2 receptor blockade (up to 80% of D_2 receptor blockade) of the nigrostriatal pathway [31,32]. Another possible side-effect is hyperprolactinaemia, caused by D_2 receptor blockade of the anterior pituitary, which can result in osteoporosis [33,34].

In the 1990's, the introduction of the second-generation "atypical" antipsychotics such as clozapine was a turning point for treatment of schizophrenia. In contrast to first-generation antipsychotics, they have less side effects on motor function and could potentially decrease both negative and positive symptoms. A main drawback of atypical antipsychotics is that they have important metabolic side effects like weight gain or diabetes [4,27,29]. Second-generation antipsychotics have a higher affinity for 5-HT_{2A} receptors than for D_2 receptors and blocks both receptor types. Unlike typical antipsychotics, atypical antipsychotics interact with a large range of other receptors, including cholinergic and serotoninergic receptors (e.g. 5-HT_{1A}, 5-HT_3, 5-HT_6 [4,35,36]). Initially, a balanced occupancy of 5-HT_{2A} and D_2-like receptors has been proposed to play a pivotal role in their mechanism of actions [35,37].

Partial D_2-Like Receptor Agonists in Schizophrenia

Currently, aripiprazole is the only partial D_2-like receptor agonist used for schizophrenia treatment. Other agents showing *in vivo* or *in vitro* partial D_2-like receptor activity represent putative antipsychotics, e.g. bifeprunox [38], SSR181507 [39], sarizotan [40], RGH-188 [41], 3PPP [42], ACR16, OSU6162 [43]. Interestingly, the N-desmethylclozapine, the major metabolites of clozapine, is also a partial D_2-like agonist.

There have been several arguments for the use of partial blockade of D_2-like receptors rather than a full blockade. First, antipsychotics like haloperidol act as D_2-like receptor blockers and at low dose increase the firing activity of DA neurons. However, at high dose they induce an inactivation via a mechanism named "depolarization block" [44,45]. Hence, after chronic treatment, the number of spontaneous active DA neurons is decreased in the VTA, reducing mesolimbic DA transmission [46,47]. In contrast to haloperidol, D_2 receptor partial agonists like aripiprazole moderately decrease VTA DA neuronal firing [38,48,49]. Chronic administration of aripiprazole does not affect neuronal firing [48,50]. Rather than the depolarization-block inactivation process, it has been suggested that partial DA receptor agonists induce a stabilization of the DA neurotransmission [6,7,37,51,52]. Aripiprazole and bifeprunox showed a stronger effect on phasic activity (i.e. on bursting) than on tonic activity (i.e. firing) [38] which can be of therapeutic interest [53]. Indeed, the preferential action of partial D_2 receptor agonists on bursting activity might stabilize DA system via a preferential reduction of phasic DA release.

Partial DA agonists present high affinity (similar to the natural ligand) for the DA receptors but a relatively low efficacy. Consequently, their effect depends on DA concentra-

tions and thus to the receptor occupancy. In the VTA and SNc, where endogenous DA concentration is relatively low, partial DA agonists largely bind to D_2 autoreceptors and suppress the firing activity as agonists. In the striatum, where the level of DA concentration is relatively high, partial D_2 agonists suppress neuronal firing presynaptically and inhibit DA release in nerve termination whereas postsynaptically, partial D_2 agonists reduce neuronal firing [6,7]. Because partial D_2 agonist agents have a weak intrinsic activity, they do not induce full blockade at D_2 receptors in the substantia nigra and in the pituitary so they do not induce metabolic and motor side effects [54], which makes them a potential candidate for treating against positive symptoms by reducing DA neurotransmission. In preclinical studies, aripiprazole showed antagonistic activity in animal models of dopaminergic activity (e.g. blockade of apomorphine-induced stereotypy) and agonist activity in an animal model of dopaminergic hypoactivity (blockade of increased DA synthesis in reserpine-treated rats) [55]. Most of typical and classical atypical antipsychotic drugs induce increase in DA release in prefrontal cortex [56,57]. In nucleus accumbens, the typical antipsychotics like haloperidol increased DA release while the atypical antipsychotics clozapine did not [58]. Local application of DA D_2 receptor agonist, like quinpirole, inhibits release of DA in prefrontal cortex [59]. However, a decrease of DA in prefrontal cortex induces an increase of DA release in the nucleus accumbens [60]. On the other hand, aripiprazole and bifeprunox seems not modify DA release in prefrontal cortex of rodents [57,61], even if a study from Li *et al.* [62] suggests that aripiprazole may slightly increase DA release. Interestingly, bifeprunox and only high doses of aripiprazole decrease DA release in rat nucleus accumbens. One may assume that the partial inhibitory effect may restore DA system where it is hypoactive which can be relevant clinically.

5-HT_{1A} Receptor Agonists in Schizophrenia

Presynaptic 5-HT_{1A} receptors are somatodendritic autoreceptors on serotoninergic neurons of raphe nuclei. Stimulation by extracellular 5-HT or by a 5-HT_{1A} receptor agonist, suppresses the firing of 5-HT neurons. Postsynaptic 5-HT_{1A} receptors are localised on pyramidal as well as GABAergic interneurons in the hippocampus, frontal and entorhinal cortex, amygdale which have been described as key areas involved in physiopathology of schizophrenia [63]. Postmortem and PET studies have shown that 5-HT_{1A} receptors binding is increased in the frontal cortex of schizophrenic patients ([64-66]; for a review see [67]). Nevertheless, a more recent imaging study using PET failed to demonstrate differences in binding of 5-HT_{1A} receptors in schizophrenic patients compared to healthy subjects [68].

Several compounds including clozapine, ziprasidone and quetiapine have a partial agonistic effect on 5-HT_{1A} receptors [69]. Recent drugs developed as potential antipsychotics, such as bifeprunox, aripiprazole [38], SSR181507, F15063 [39], present a more potent 5-HT_{1A} receptor agonistic effect. Preclinical and clinical studies have evaluated the effect of 5-HT_{1A} agonists on schizophrenia symptoms. For example, the 5-HT_{1A} receptor agonist 8-OH-DPAT increased the effect of the D_2-like antagonist raclopride in the conditioned avoidance response (a test used to evaluate an antipsychotic-like effect). The same effect has been observed with haloperidol [70]. Similarly, clinical studies have shown a beneficial effect on psychotic syndromes by simultaneous administration of haloperidol (a typical antipsychotic) and buspirone (a partial 5-HT_{1A} receptor agonists) [71,72].

Historically, the 5-HT_{2A} receptor has been a major target for the development of antipsychotics. It has been shown that antagonism at 5-HT_{2A} receptor coupled to weaker antagonism of DA D_2 receptors increases the release of DA in the prefrontal cortex (PFC) [73, 74] which may contribute to improved cognition in schizophrenic patients [75]. Importantly, 5-HT_{1A} receptors seem to modulate DA transmission in the PFC in a way similar to 5-HT_{2A} receptor antagonists [67,76-79]. For example, the 5-HT_{1A} agonist 8-OHDPAT increases DA release in this brain area [79-81]. Also, the atypical antipsychotics clozapine and olanzapine (acting as a 5-HT_{1A} receptor agonist and a 5-HT_{2A} antagonist) increase DA release [57,79,82], whereas haloperidol does not [57,83]. Interestingly, administration of the selective 5-HT_{1A} receptor antagonist WAY-100635 reverses the effect of risperidone and olanzapine which do have not a direct action on 5-HT_{1A} receptors [57,82]; [81,84,85]. This effect is blocked by local injection of 5-HT_{1A} antagonist in the mPFC and by a cortical hemi-transection [86], suggesting a mediating role for presynaptic receptors. This suggests that direct or indirect 5-HT_{1A} receptor stimulation may increase DA release in prefrontal cortex.

It has been reported that cognitive impairments are associated with a decrease of DA release in PFC. Clinical studies have reported a beneficial therapeutic effect of the simultaneously administration of a typical or atypical antipsychotic and a 5-HT_{1A} agonist (like tandospirone or buspirone) on cognitive deficits, including verbal learning and memory (see for review [63]). Contrary to this finding, is a study that reported the impaired cognition in healthy volunteers following 5-HT_{1A} agonist administration [87]. In sum, it seems that of 5-HT_{1A} receptor stimulation may ameliorate cognitive deficits in schizophrenia (see for review [63,67,88]).

Schizophrenia is often associated with idem affective disorders [89,90]. 5-HT_{1A} agonists induce anxiolytic and antidepressive effects in clinical studies, which makes them potentially interesting for treatment of major depression [91]. In this regard, compounds such as aripiprazole present anxiolytic effects in preclinical tests of anxiety [38,92,93].

It has been proposed that 65% of D_2 receptors occupancy is necessary for clinical efficacy of treating psychotics, while it must not exceed 80% in order to avoid EPS. Therefore, it is important to develop compounds able to increase this narrow window [31,32]. 5-HT_{1A} receptor agonists can play a role herein [94]. In a preclinical study, administration of the 5-HT_{1A} agonist 8-OH-DPAT reversed the catalepsy induced by D_2 receptor antagonists or antipsychotics, by stimulation of the 5-HT_{1A} autoreceptor in the median raphe nuclei [95-97]. In monkeys, 8-OH-DPAT also reduced haloperidol-induced extrapyramidal side effects [98]. A clinical study has demonstrated the same results with the 5-HT_{1A} receptor agonist buspirone [71]. Interestingly, it has been shown that F15063, SLV313 and bifeprunox, which are potential antipsychotics with a 5-HT_{1A} agonistic activity, induced catalepsy only in presence of the 5-HT_{1A} antagonist WAY-100,635. However, the potential antipsychotic SSR-181507 (a 5-HT_{1A} receptor agonist) did not induce catalepsy after administra-

tion of WAY-100,536, suggesting that alternative anti-cataleptic mechanisms may exist [99]. Finally, there is strong evidence that that stimulation of 5-HT_{1A} receptors may reduce EPS [97].

Based on these results, we hypothesize that co-administration of a partial 5HT_{1A} receptor agonist and a partial D2-like agonist improves the pharmacological profile of administration of a partial D2- like agonist alone, because co-administration could result in a combined reduced risk of EPS and reduced cognitive disturbances in schizophrenic patients, and potentially improved mood [67,100].

PARTIAL DOPAMINE D_2/SEROTONIN 5-HT_{1A} RECEPTOR AGONISTS AND AFFECTIVE DISORDERS

Major Depression

With a lifetime prevalence rate of more than 12% in men and 20% in women, major depression is the most common psychiatric disorder [101,102]. The diagnosis of major depressive disorder requires a distinct change in mood, characterized by sadness or irritability and accompanied by several psychophysiological changes, such as sleep disorders, weight loss or weight gain, decreased interest of pleasure stimuli (e.g. sex, food, social interaction), decreased ability to concentrate, and recurrent thoughts of death and suicide [102]. Although the pathophysiology of depression is poorly understood, the development of different classes of antidepressants during the last four decades was accompanied by the emergence of theories based on deficiencies of central aminergic systems [102]. These theories propose that a deficiency of the cerebral neurotransmission of monoamines would be the underlying cause of depression. Although involvement of catecholamines (noradrenaline and DA) in the effects of antidepressants cannot be excluded, the vast majority of pre-clinical data point toward a central role of 5-HT [103]. This is supported by the success of selective serotonin reuptake inhibitors (SSRIs) as first-line therapy. SSRIs directly act on 5-HT transporter and block its reuptake, leading to enhanced 5-HT neurotransmission [104]. In accordance, depletion of the 5-HT precursor L-tryptophan produces a rapid relapse of depression in patients who have been successfully treated with a SSRI [105].

Therapeutic agents for Major Depression

Even though first generation antidepressant therapy with tricyclic antidepressants and monoamine oxydase inhibitors (IMAO) reduced inhibitors reduced symptoms of depression, their side effects (hypotension, retention urinary, sexual and sleep impairment) and toxicity lead to the search for more tolerable and safe antidepressants. More recent drugs such as SSRIs, selective noradrenaline reuptake inhibitors, noradrenaline and serotonin reuptake inhibitors or atypical antidepressants (such as mirtazapine or agomelatine), have fewer and less severe side effects than these first generation drugs due to their lack of affinity for amines and acetylcholine receptors [106]. In spite of this wide variety of medications available, however, current treatments of depression with pharmacotherapy remains unsatisfactory [107]. Two major problems remain unresolved. First, one-third of the patients does not respond to any treatment and one-third shows only a partial response to any first agent used at an adequate dose for a sufficient time. Second, there is an undesirable 3-8 weeks delay before the onset of therapeutic response to antidepressant drugs. This period of time is of particular relevance, since it is associated with an augmentation of risk of suicide [108]. These two problems stipulate the need and urgency to intensify research in order to develop more efficacious treatments and to reduce the delay in treatment response [109,110]. The current prevalent strategy is the development of drugs with dual or triples modes of action, e.g. vilazodone (a 5-HT reuptake inhibitor and 5-HT_{1A} receptor partial agonist [111]), or to target 5-HT receptor subtypes, e.g. 5-HT_6 receptors or 5-HT_{2C} receptors [112]. Other 5-HT receptors agonists or antagonists i.e. 5-HT_4 et 5-HT_7 receptor have also been evaluated in preclinical studies [113,114].

D_2-Like Receptor Agonists in Major Depression

Recent studies suggest that various atypical antipsychotics can be effective as anti-manic (see below) or antidepressant agents, and therefore they are increasingly popular as adjunctive agents in clinical therapy. For example, olanzapine combined with fluoxetine significantly improved depressive symptoms compared to patients treated with olanzapine or fluoxetine alone [115-117]. In a similar fashion, combined administration of risperidone and citalopram enhanced the antidepressant response in treatment-resistant patients [118]. Aripiprazole, which acts as a partial D_2 and 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist, seems a promising agent for the treatment of depression for two reasons. First, short- and long-term treatment with this compound enhances 5-HT neurotransmission by increasing the spontaneous firing of 5-HT neurons via 5-HT_{1A} autoreceptors desensitization [50]. Second, a number of studies have reported that partial D_2 receptor agonists are effective adjuncts in treatment-resistant depression [119,120] and potentiate the effect of SSRIs [121,122]. It has been shown that aripiprazole is well tolerated and effective in improving response rates in patients with major depressive disorders who show an incomplete response to antidepressant therapy. Remission rates were about 10% higher when aripiprazole is used as an adjuvant of antidepressant treatment [123-125].

5-HT_{1A} Receptor Agonists in Major Depression

Acute and short-term administration of 5-HT_{1A} receptors agonists induce a decrease of 5-HT neuronal activity, a decreased 5-HT release in postsynaptic structures, and a direct occupation of the postsynaptic 5-HT_{1A} receptors [126,127]. During chronic treatment, 5-HT neurons gradually recover their normal firing rate as a result of 5-HT_{1A} autoreceptor desensitization [128-130]. This gradual recovery of 5-HT neuronal activity may explain the therapeutic delay of clinical action of these drugs. Preclinical data suggest that postsynaptic 5-HT_{1A} receptors are particularly important for the antidepressant response. First, the activation of these receptors leads to behavioral changes in several animal models, such as the forced swim test (FST), similar to those observed with conventional antidepressants [131]. Second, there is evidence that neurogenesis, which is a crucial phenomenon in the antidepressant action, can be mediated via 5-HT_{1A} receptor activation [132,133]. These results support the hypothesis that an enhancement of 5-HT_{1A} neurotransmission underlies the antidepressant response [134-137]. Partial 5-HT_{1A} receptor agonists present high affinity (similar to the

endogenous ligand) for the 5-HT_{1A} receptors, but a relatively low efficacy. As a result, their effect is dependent on the intrinsic concentration of 5-HT and thus to the receptor occupancy. In depressed patients, partial 5-HT rceptor agonists are thought to increase the 5-HT neurotransmission in postsynaptic structures (in the cortex and the limbic areas) because of the low 5-HT tone. Indeed, the exogenous partial agonist, such as buspirone or gepirone, would not compete but act in synergy with the endogenous transmitter. Partial agonists can modulate their action (act as agonist or antagonist) according to the state of 5-HT neurotransmission and thus can regulate with perceptiveness this function.

The azapirones (gepirone, buspirone, tandospirone and ipsapirone) which act as partial 5-HT_{1A} receptor agonist [129,138] have shown efficacy in the treatment of anxiety [139] and major depression [140-142]. Buspirone is a commercially agent available but used as a single agent appears to be non-effective [143]. Early clinical trials conducted with an immediate release (IR) formulation of gepirone, buspirone and ipsapirone showed antidepressant efficacy after eight weeks [141,144], but has the disadvantages of poor tolerability (dizziness, nausea, insomnia, headache and asthenia [91]) and a limited efficacy (short half-life and rapid absorption from the gastrointestinal tract). More recently, azapirones have been reformulated as an extended-release (ER) tablet which increases their half life, allowing more gradual and sustained absorption from the gastrointestinal tract while lowering peak plasma gepirone concentration [145]. Wilcox *et al*. [146] showed that gepirone ER administration had antidepressant efficacy 1 week until 6 weeks of treatment with a daily dose of 70mg but not with 40mg. More recently, several studies also demonstrated the short-term and the long-term effectiveness of gepirone ER administration [140,147,148]. Interestingly, gepirone IR and ER administration seems to be effective to prevent relapse in major depression [148,149]. In conclusion, ER administration improves the tolerability and enhances the effectiveness of azapirones [150].

While these results from clinical trials support the efficacy and the tolerability of ER formulation of gepirone in major depressive disorder, it should be noted that results are less conclusive concerning other azapirones (buspirone and ipsapirone). In addition, azapirones are rapidly metabolized into 1-(2-pyrimidinyl)-piperazine (1-PP) which is an alpha-2 adrenoreceptor antagonist, like mirtazapine [134,151] an effective antidepressant drug. However, the antidepressant-like effect of 1-PP is not well established [131,152,153].

Bipolar Disorder

Bipolar disorder is a severe chronic illness associated with abnormal structure and function of the central nervous system with high rates of recurrence, disability, social impairment, and suicide that affects about 1-6% of the population. Although the disorder is defined by sequentially occurrence of manic and depressive episodes, the depressive episodes are the more handicapping aspect of the illness. Specifically, the depressive episodes are more numerous, last longer, and are less responsive to treatment than the manic episodes [154].

Therapeutic Agents for Bipolar Disorder

The origin of this psychiatric disorder seems to be an excessive cellular excitation. The goals of pharmacological treatments for bipolar disorder are, first, to decrease this hyperexcitability and stabilize mood, and second, to prevent the recurrence of depressive and manic episodes. Traditional mood-stabilizing agents such as lithium and anticonvulsive agents (valproate or lamotrigine) are currently used as first-line medications for the treatment of manic episodes, but there is a lack of treatment for bipolar depressive episodes. These agents yield inadequate responses to about 20-40% of the patients and have severe side effects such as tremors, gastrointestinal disorders, tiredness, somnolence, and cognitive impairment in memory and concentration..

Because of these limitations of current treatments of bipolar disorder, the use of antipsychotics and other psychotropic agents has been investigated [155]. Short-term studies (3-4 weeks) suggest that atypical antipsychotics (olenzapine, risperidone, ziprasidone) have beneficial effects on manic ([156-159] and depressive episodes [160]. However, few studies have been conducted to demonstrate the continued efficacy of these agents as monotherapy for longer-term management of bipolar disorder. For example, a placebo-controlled study showed maintenance of the efficacy of risperidone monotherapy over 12 weeks [161] and aripiprazole seems to have similar effects.

Partial D_2-Like Receptor Agonists in Manic Episodes

Studies have demonstrated that aripiprazole is effective and well tolerated in the treatment of acute bipolar mania [162,163]. Aripiprazole had superior efficacy to haloperidol in response rates and tolerability in a 12-week acute mania trial in patients with bipolar I disorder in acute manic or mixed episodes [164]. Furthermore, aripiprazole monotherapy was superior to placebo in maintaining efficacy in patients with a recent manic/mixed episode who were stabilized and maintained on a regimen of aripiprazole for 12 weeks [164-166], 26 weeks [167] and 100 weeks [168]. Vieta *et al*. [169] demonstrated that adjunctive aripiprazole therapy to lithium or valproate showed significant improvements in mania symptoms from one week in bipolar patients with manic or mixed episodes who were partially nonresponsive to lithium/valproate monotherapy. The same result has been observed with other atypical antipsychotics. The use of risperidone [170], olanzapine [171] and quetiapine [172] as adjunctive agent enhanced the response to classical treatment. While the beneficial effect of aripiprazole was clear in the treatment of manic episodes, there is no evidence that aripiprazole monotherapy has superior efficacy compared to placebo treatment at the end of the treatment in bipolar depression at the dose use [160]. Furthermore, aripiprazole has important side effects such as akathisia, insomnia, nausea, restless or dry mouth [160].

PARTIAL DOPAMINE D_2/SEROTONIN 5-HT_{1A} RECEPTOR AGONISTS AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a very frequent neurodegenerative disease that results from the loss of dopaminergic cells in the SNc and is mainly characterized by motor defi-

cits including bradykinesia, tremors and muscular rigidity [173]. Moreover, with the increasing of lifetime expectancy, the number of people with PD will dramatically increase in the future.

Therapeutic Agents for Parkinson's Disease

Currently, PD pharmacotherapy is based on restorating dopaminergic function [174,175]. While L-dihydroxyphenylalanine (L-DOPA) is presently the most effective treatment for PD, its use is associated with a high probability of motor complications, including abnormal involuntary movements (dyskinesia) and motor fluctuations in 50% of PD patients [176,177]. It has conducted clinicians to delay the initiation of L-DOPA treatment by prior treatment with DA receptor agonists, including bromocriptine, pergolide, pramipexole, ropinirole or pardoprunox. These drugs have been used for antiparkinsonian monotherapy in early stages of PD, or in combination with L-DOPA, in order to decrease the incidence of response fluctuations and dyskinesias [178-181]. However, these dopaminergic therapies can elicit psychiatric complications such as pathological gambling or somnolence [182,183]. Hence, there is an urgent need for new compounds with fewer side effects [182,184,185].

Partial D_2-Like Receptor Agonists in PD

D_2-like receptors are abundant in motor areas such as the basal ganglia. The highest density of dopaminergic receptors in the VTA and SNc corresponds to the D_2 subtype, whereas the D_3 subtype only exhibits a moderate density and the D_4 subtype appears to be absent in these neuronal structures [9,186]. In contrast, D_3 and D_4 receptors are located in limbic and cortical areas and may contribute to the psychiatric disturbances occurring with DA agonists and L-DOPA therapeutics. Hence, the major receptor subtype involved in mediating local effects of DA in the VTA seems to be the D_2 autoreceptor [8,187] whereas D_1 and possibly D_3 receptors may play a less important role in controlling DA neuronal firing and release [9-11]. Accordingly, an *in vitro* electrophysiological study has shown that DA fails to inhibit dopaminergic neuronal activity from D_2 receptor-deficient mice [188].

Full DA receptor agonists can induce dyskinesia and psychotic-like symptoms including hallucinations (probably due to the overstimulation of extra-striatal DA receptors) or somnolence [189,190]. It has been suggested that such side-effects could be counteracted by the use of partial D_2-like receptor agonists [191]. These compounds might stimulate D_2 and D_3 receptors when the dopaminergic tone is low, while counteracting excessive stimulation of the DA D_2 and D_3 receptor when the dopaminergic tone is high [191]. It is also possible that partial agonists would modulate dopaminergic transmission in a specific region, resulting in the restoration of dopaminergic transmission which is perturbed in PD patients [191]. The primary motor symptoms of PD could potentially be treated by moderate stimulation of striatal DA receptors, while not maximally stimulating these receptors (which is thought to account for the development of dyskinesia in PD patients [190]). Furthermore, preventing psychosis-like symptoms using partial DA receptor agonists might be possible since they would not maximally stimulate dopaminergic receptors in mesolimbic and mesocortical pathways [178,192].

5-HT_{1A} Receptor Agonists in PD

5-HT_{1A} receptor agonists could reduce the incidence of dyskinesia. The 5-HT_{1A} receptor agonist tandospirone reduced dyskinesia in L-DOPA-treated PD patients [193]. More recently, preclinical and clinical studies suggest that sarizotan, a 5-HT_{1A} receptor agonist that possesses weak D_3 and D_4 receptor agonist activity, could ameliorate dyskinetic symptoms in association with L-DOPA [194,195].

It has been suggested that the neurodegenerative processes underlying PD result from loss of 5-HT input from the DRN to the striatum [196]. L-DOPA may be converted to DA in remaining serotonergic neurons and the non-physiological release of DA may lead to abnormal DA receptor stimulation in the striatopallidal pathways, in turn resulting in the generation of L-DOPA-induced dyskinesia [196]. Suppressing the activity of 5-HT inputs to the striatum via presynaptic 5-HT_{1A} agonists may reduce L-DOPA-induced dyskinesia. Studies with 5-HT_{1A} agonists have suggested a reduction in L-DOPA-induced dyskinesia but a worse PD disability [197]. Importantly, Carta *et al.* [196] have shown that dyskinesia induced by chronic L-DOPA treatment in rats with 6-OHDA-induced lesions of the nigrostriatal DA pathway is critically dependent on the integrity and function of the serotonergic system. Removal of the 5-HT afferents or dampening 5-HT neuronal activity by 5-HT_{1A} and 5-HT_{1B} agonist ligands, resulted in a blockade of the L-DOPA-induced dyskinesias, suggesting that dysregulated DA release from 5-HT terminals is the "prime trigger" of dyskinesia in the rat PD model. In animals with complete DA lesions, the spared 5-HT innervation was unable to sustain the therapeutic effect of L-DOPA, suggesting that DA released as a "false transmitter" from 5-HT terminals is detrimental rather than beneficial. The potent synergistic effect of low doses of 5-HT_{1A} and 5-HT_{1B} agonists to suppress dyskinesia, without affecting the anti-parkinsonian effect of L-DOPA in presence of spared DA terminals, suggests that early use of these drugs could counteract the development of dyskinesia in PD patients [196]. Interestingly, 5-HT dysfunction can also be observed in 6-OHDA-lesioned rats. Wang et. al. [198] have shown that unilateral lesion of the rat nigrostriatal pathway induces an increase of neuronal firing of 5-HT neurons associated with desensitized 5-HT_{1A} autoreceptors. Moreover, the degeneration of the nigrostriatal pathway leads to a marked reduction of 5-HT_{1A} receptor density in the hippocampal formation, midbrain raphe nuclei and prefrontal cortex of the MPTP-treated monkeys and PD patients [199,200]. Conversely, high frequency stimulation of the subthalamus nucleus, a well admit antiparkinsonian therapy, has been shown to reduce 5-HT neuronal firing [201], further suggesting the involvement of 5-HT system in the pathophysiology of PD. Finally and as mentioned above, one may assume that 5-HT_{1A} agonism may be also beneficial against depression and cognitive impairment frequently observed in PD patients [202,203].

CONCLUSION

In this review, focus has been placed on the putative therapeutic benefit of partial dopamine D_2 and serotonin 5-HT_{1A} receptors agonists in the treatment of schizophrenia,

major depression, bipolar disorders and Parkinson's disease. While several studies are in accordance with the marked interest of partial D_2/5-HT_{1A} agonists in reducing side effects i.e. extrapyramidal symptoms and cognitive impairments in schizophrenia, various researches are still needed to emphasize their beneficial utility in major depression, bipolar disorders and Parkinson's disease. Treatment with aripiprazole in major depression as monotherapy or as adjuvant with a classical antidepressants seems to improve the antidepressant response whereas, in bipolar disorder, only partial dopamine D_2 receptors agonists show advantages in the treatment of manic episodes. Differently, if treatment of Parkinson's disease with partial D_2 and 5-HT_{1A} receptors agonists is still at the experimental phase, increasing studies report a decrease of side effects with these drugs. Hence, these relatively recent researches provide an exciting future in the discovery of novel stabilizators agents for the management of the latter diseases.

ACKNOWLEDGEMENT

Helpful comments from Chris A. Oosterhof and Nick N. Oosterhof were gratefully acknowledged.

REFERENCES

[1] Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007; 64(3): 327-37.

[2] Kalivas PW. Cocaine and amphetamine-like psychostimulants: neurocircuitry and glutamate neuroplasticity. Dialogues Clin Neurosci 2007; 9(4): 389-97.

[3] Laviolette SR. Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? Schizophr Bull 2007; 33(4): 971-81.

[4] Abi-Dargham A, Laruelle M. Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. Eur Psychiatry 2005; 20(1): 15-27.

[5] Halbreich U, Kinon BJ, Gilmore JA, Kahn LS. Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects. Psychoneuroendocrinology 2003; 28 (Suppl 1): 53-67.

[6] Tamminga CA. Partial dopamine agonists in the treatment of psychosis. J Neural Transm 2002; 109(3): 411-20.

[7] Inoue A, Nakata Y. Strategy for modulation of central dopamine transmission based on the partial agonist concept in schizophrenia therapy. Jpn J Pharmacol 2001; 86(4): 376-80.

[8] Etievant A, Betry C, Arnt J, Haddjeri N. Bifeprunox and aripiprazole suppress *in vivo* VTA dopaminergic neuronal activity via D2 and not D3 dopamine autoreceptor activation. Neurosci Lett 2009; 460(1): 82-6.

[9] Adell A, Artigas F. The somatodendritic release of dopamine in the ventral tegmental area and its regulation by afferent transmitter systems. Neurosci Biobehav Rev 2004; 28(4): 415-31.

[10] Smith Y, Kieval JZ. Anatomy of the dopamine system in the basal ganglia. Trends Neurosci 2000; 23 (Suppl 10): S28-33.

[11] Millan MJ, Gobert A, Newman-Tancredi A, *et al.* S33084, a novel, potent, selective, and competitive antagonist at dopamine D(3)-receptors: I. Receptorial, electrophysiological and neurochemical profile compared with GR218,231 and L741,626. J Pharmacol Exp Ther 2000; 293(3): 1048-62.

[12] Grace AA, Bunney BS. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons--1. Identification and characterization. Neuroscience 1983; 10(2): 301-15.

[13] Floresco SB, West AR, Ash B, Moore H, Grace AA. Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nat Neurosci 2003; 6(9): 968-73.

[14] Gonon FG. Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by *in vivo* electrochemistry. Neuroscience 1988; 24(1): 19-28.

[15] Dahlstrom A, Fuxe K. Localization of monoamines in the lower brain stem. Experientia 1964; 20(7): 398-9.

[16] Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev 1992; 72(1): 165-229.

[17] Wiklund L, Bjorklund A. Mechanisms of regrowth in the bulbospinal serotonin system following 5,6-dihydroxytryptamine induced axotomy. II. Fluorescence histochemical observations. Brain Res 1980; 191(1): 109-27.

[18] Descarries L, Watkins KC, Garcia S, Beaudet A. The serotonin neurons in nucleus raphe dorsalis of adult rat: a light and electron microscope radioautographic study. J Comp Neurol 1982; 207(3): 239-54.

[19] Baker PC, Hoff KM. Chronic citalopram action and the maturing mouse brain's indoleamine levels. Gen Pharmacol 1990; 21(5): 703-7.

[20] Moss MS, Basbaum AI. The peptidergic organization of the cat periaqueductal gray. II. The distribution of immunoreactive substance P and vasoactive intestinal polypeptide. J Neurosci 1983; 3(7): 1437-49.

[21] Descarries L, Berthelet F, Garcia S, Beaudet A. Dopaminergic projection from nucleus raphe dorsalis to neostriatum in the rat. J Comp Neurol 1986; 249(4): 511-20, 484-5.

[22] Harandi M, Aguera M, Gamrani H, *et al.* gamma-Aminobutyric acid and 5-hydroxytryptamine interrelationship in the rat nucleus raphe dorsalis: combination of radioautographic and immunocytochemical techniques at light and electron microscopy levels. Neuroscience 1987; 21(1): 237-51.

[23] Gaddum JH, Picarelli ZP. Two kinds of tryptamine receptor. Br J Pharmacol Chemother 1957; 12(3): 323-8.

[24] Humphrey PP, Hartig P, Hoyer D. A proposed new nomenclature for 5-HT receptors. Trends Pharmacol Sci 1993; 14(6): 233-6.

[25] Aghajanian GK, Lakoski JM. Hyperpolarization of serotonergic neurons by serotonin and LSD: studies in brain slices showing increased K+ conductance. Brain Res 1984; 305(1): 181-5.

[26] Rueter LE, Fornal CA, Jacobs BL. A critical review of 5-HT brain microdialysis and behavior. Rev Neurosci 1997; 8(2): 117-37.

[27] Schultz SH, North SW, Shields CG. Schizophrenia: a review. Am Fam Physician 2007; 75(12): 1821-9.

[28] Meltzer HY, Park S, Kessler R. Cognition, schizophrenia, and the atypical antipsychotic drugs. Proc Natl Acad Sci USA 1999; 96(24): 13591-3.

[29] Walker E, Kestler L, Bollini A, Hochman KM. Schizophrenia: etiology and course. Annu Rev Psychol 2004; 55: 401-30.

[30] Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. Annu Rev Pharmacol Toxicol 2001; 41: 237-60.

[31] Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 1976; 261(5562): 717-9.

[32] Seeman P, Kapur S. Schizophrenia: more dopamine, more D2 receptors. Proc Natl Acad Sci USA 2000; 97(14): 7673-5.

[33] Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. Drugs 2004; 64(20): 2291-314.

[34] O'Keane V. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. J Psychopharmacol 2008; 22 (Suppl. 2): 70-5.

[35] Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther 1989; 251(1): 238-46.

[36] Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 2005; 10(1): 79-104.

[37] Shapiro DA, Renock S, Arrington E, *et al.* Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28(8): 1400-11.

[38] Dahan L, Husum H, Mnie-Filali O, Arnt J, Hertel P, Haddjeri N. Effects of bifeprunox and aripiprazole on rat serotonin and dopamine neuronal activity and anxiolytic behaviour. J Psychopharmacol 2009; 23(2): 177-89.

[39] Assie MB, Mnie-Filali O, Ravailhe V, *et al.* F15063, a potential antipsychotic with dopamine D2/D3 receptor antagonist, 5-HT1A receptor agonist and dopamine D4 receptor partial agonist proper-

ties: influence on neuronal firing and neurotransmitter release. Eur J Pharmacol 2009; 607(1-3): 74-83.

[40] Bartoszyk GD, Van Amsterdam C, Greiner HE, Rautenberg W, Russ H, Seyfried CA. Sarizotan, a serotonin 5-HT1A receptor agonist and dopamine receptor ligand. 1. Neurochemical profile. J Neural Transm 2004; 111(2): 113-26.

[41] Gyertyán I, Kiss B, Sághy K, *et al.* Pharmacological profile of RGH-188, a novel dopamine D3/D2 receptor antagonist/partial agonist atypical antipsychotic. Papers of the 19th ECNP Congress 2006; 16 (Suppl 4): S432.

[42] Lahti AC, Weiler MA, Corey PK, Lahti RA, Carlsson A, Tamminga CA. Antipsychotic properties of the partial dopamine agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine(preclamol) in schizophrenia. Biol Psychiatry 1998; 43(1): 2-11.

[43] Natesan S, Svensson KA, Reckless GE, *et al*. The dopamine stabilizers (S)-(-)-(3-methanesulfonyl-phenyl)-1-propyl-piperidine [(-)-OSU6162] and 4-(3-methanesulfonylphenyl)-1-propyl-piperidine (ACR16) show high *in vivo* D2 receptor occupancy, antipsychotic-like efficacy, and low potential for motor side effects in the rat. J Pharmacol Exp Ther 2006; 318(2): 810-8.

[44] Hand TH, Hu XT, Wang RY. Differential effects of acute clozapine and haloperidol on the activity of ventral tegmental (A10) and nigrostriatal (A9) dopamine neurons. Brain Res 1987; 415(2): 257-69.

[45] Grace AA, Bunney BS, Moore H, Todd CL. Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. Trends Neurosci 1997; 20(1): 31-7.

[46] Chiodo LA, Bunney BS. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. J Neurosci 1983; 3(8): 1607-19.

[47] White FJ, Wang RY. Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. Science 1983; 221(4615): 1054-7.

[48] Bortolozzi A, Diaz-Mataix L, Toth M, Celada P, Artigas F. *In vivo* actions of aripiprazole on serotonergic and dopaminergic systems in rodent brain. Psychopharmacology (Berl) 2007; 191(3): 745-58.

[49] Stark AD, Jordan S, Allers KA, *et al.* Interaction of the novel antipsychotic aripiprazole with 5-HT1A and 5-HT 2A receptors: functional receptor-binding and *in vivo* electrophysiological studies. Psychopharmacology (Berl) 2007; 190(3): 373-82.

[50] Chernoloz O, El Mansari M, Blier P. Electrophysiological studies in the rat brain on the basis for aripiprazole augmentation of antidepressants in major depressive disorder. Psychopharmacology (Berl) 2009; 206(2): 335-44.

[51] Burris KD, Molski TF, Xu C, *et al.* Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002; 302(1): 381-9.

[52] Naber D, Lambert M. Aripiprazole: a new atypical antipsychotic with a different pharmacological mechanism. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28(8): 1213-9.

[53] Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 1991; 41(1): 1-24.

[54] Hirose T, Kikuchi T. Aripiprazole, a novel antipsychotic agent: dopamine D2 receptor partial agonist. J Med Invest 2005; 52 (Suppl): 284-90.

[55] Kikuchi T, Tottori K, Uwahodo Y, *et al.* 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-qui nolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. J Pharmacol Exp Ther 1995; 274(1): 329-36.

[56] Westerink BH, de Boer P, de Vries JB, Kruse CG, Long SK. Antipsychotic drugs induce similar effects on the release of dopamine and noradrenaline in the medial prefrontal cortex of the rat brain. Eur J Pharmacol 1998; 361(1): 27-33.

[57] Assie MB, Ravailhe V, Faucillon V, Newman-Tancredi A. Contrasting contribution of 5-hydroxytryptamine 1A receptor activation to neurochemical profile of novel antipsychotics: frontocortical dopamine and hippocampal serotonin release in rat brain. J Pharmacol Exp Ther 2005; 315(1): 265-72.

[58] Karoum F, Egan MF. Dopamine release and metabolism in the rat frontal cortex, nucleus accumbens, and striatum: a comparison of acute clozapine and haloperidol. Br J Pharmacol 1992; 105(3): 703-7.

[59] Santiago M, Machado A, Cano J. Regulation of prefrontal cortical dopamine release by dopamine receptor agonists and antagonists. Eur J Pharmacol 1993; 239(1-3): 83-91.

[60] King D, Zigmond MJ, Finlay JM. Effects of dopamine depletion in the medial prefrontal cortex on the stress-induced increase in extracellular dopamine in the nucleus accumbens core and shell. Neuroscience 1997; 77(1): 141-53.

[61] Jordan S, Koprivica V, Dunn R, Tottori K, Kikuchi T, Altar CA. *In vivo* effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function. Eur J Pharmacol 2004; 483(1): 45-53.

[62] Li Z, Ichikawa J, Dai J, Meltzer HY. Aripiprazole, a novel antipsychotic drug, preferentially increases dopamine release in the prefrontal cortex and hippocampus in rat brain. Eur J Pharmacol 2004; 493(1-3): 75-83.

[63] Meltzer HY, Sumiyoshi T. Does stimulation of 5-HT(1A) receptors improve cognition in schizophrenia? Behav Brain Res 2008; 195(1): 98-102.

[64] Hashimoto T, Nishino N, Nakai H, Tanaka C. Increase in serotonin 5-HT1A receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. Life Sci 1991; 48(4): 355-63.

[65] Burnet PW, Eastwood SL, Harrison PJ. 5-HT1A and 5-HT2A receptor mRNAs and binding site densities are differentially altered in schizophrenia. Neuropsychopharmacology 1996; 15(5): 442-55.

[66] Kasper S, Tauscher J, Willeit M, *et al.* Receptor and transporter imaging studies in schizophrenia, depression, bulimia and Tourette's disorder--implications for psychopharmacology. World J Biol Psychiatry 2002; 3(3): 133-46.

[67] Millan MJ. Improving the treatment of schizophrenia: focus on serotonin (5-HT)(1A) receptors. J Pharmacol Exp Ther 2000; 295(3): 853-61.

[68] Frankle WG, Lombardo I, Kegeles LS, *et al.* Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [11C]WAY 100635. Psychopharmacology (Berl) 2006; 189(2): 155-64.

[69] Newman-Tancredi A, Gavaudan S, Conte C, *et al.* Agonist and antagonist actions of antipsychotic agents at 5-HT1A receptors: a [35S]GTPgammaS binding study. Eur J Pharmacol 1998; 355(2-3): 245-56.

[70] Prinssen EP, Kleven MS, Koek W. Effects of dopamine antagonists in a two-way active avoidance procedure in rats: interactions with 8-OH-DPAT, ritanserin, and prazosin. Psychopharmacology (Berl) 1996; 128(2): 191-7.

[71] Goff DC, Midha KK, Brotman AW, McCormick S, Waites M, Amico ET. An open trial of buspirone added to neuroleptics in schizophrenic patients. J Clin Psychopharmacol 1991; 11(3): 193-7.

[72] Sirota P, Epstein B, Benatov R, Sousnostzky M, Kindler S. An open study of buspirone augmentation of neuroleptics in patients with schizophrenia. J Clin Psychopharmacol 2001; 21(4): 454-5.

[73] Moghaddam B, Bunney BS. Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an *in vivo* microdialysis study. J Neurochem 1990; 54(5): 1755-60.

[74] Kuroki T, Meltzer HY, Ichikawa J. Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J Pharmacol Exp Ther 1999; 288(2): 774-81.

[75] Meltzer HY, Huang M. *In vivo* actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res 2008; 172: 177-97.

[76] Tanda G, Carboni E, Frau R, Di Chiara G. Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? Psychopharmacology (Berl) 1994; 115(1-2): 285-8.

[77] Kuroki T, Ichikawa J, Dai J, Meltzer HY. R(+)-8-OH-DPAT, a 5-HT1A receptor ago]nist, inhibits amphetamine-induced serotonin and dopamine release in rat medial prefrontal cortex. Brain Res 1996; 743(1-2): 357-61.

[78] Sakaue M, Somboonthum P, Nishihara B, *et al.* Postsynaptic 5-hydroxytryptamine(1A) receptor activation increases *in vivo* dopamine release in rat prefrontal cortex. Br J Pharmacol 2000; 129(5): 1028-34.

[79] Rollema H, Lu Y, Schmidt AW, Sprouse JS, Zorn SH. 5-HT(1A) receptor activation contributes to ziprasidone-induced dopamine release in the rat prefrontal cortex. Biol Psychiatry 2000; 48(3): 229-37.

[80] Arborelius L, Nomikos GG, Hacksell U, Svensson TH. (R)-8-OH-DPAT preferentially increases dopamine release in rat medial prefrontal cortex. Acta Physiol Scand 1993; 148(4): 465-6.

[81] Ichikawa J, Li Z, Dai J, Meltzer HY. Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. Brain Res 2002; 956(2): 349-57.

[82] Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY. 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001; 76(5): 1521-31.

[83] Volonte M, Monferini E, Cerutti M, Fodritto F, Borsini F. BIMG 80, a novel potential antipsychotic drug: evidence for multireceptor actions and preferential release of dopamine in prefrontal cortex. J Neurochem 1997; 69(1): 182-90.

[84] Rollema H, Lu Y, Schmidt AW, Zorn SH. Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation. Eur J Pharmacol 1997; 338(2): R3-5.

[85] Chung YC, Li Z, Dai J, Meltzer HY, Ichikawa J. Clozapine increases both acetylcholine and dopamine release in rat ventral hippocampus: role of 5-HT1A receptor agonism. Brain Res 2004; 1023(1): 54-63.

[86] Diaz-Mataix L, Scorza MC, Bortolozzi A, Toth M, Celada P, Artigas F. Involvement of 5-HT1A receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. J Neurosci 2005; 25(47): 10831-43.

[87] Yasuno F, Suhara T, Nakayama T, *et al*. Inhibitory effect of hippocampal 5-HT1A receptors on human explicit memory. Am J Psychiatry 2003; 160 (2): 334-40.

[88] Bantick RA, Deakin JF, Grasby PM. The 5-HT1A receptor in schizophrenia: a promising target for novel atypical neuroleptics? J Psychopharmacol 2001; 15(1): 37-46.

[89] Siris SG. Depression in schizophrenia: perspective in the era of "Atypical" antipsychotic agents. Am J Psychiatry 2000; 157(9): 1379-89.

[90] Keck PE Jr., Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000; 61 (Suppl. 3): 4-9.

[91] Blier P, Ward NM. Is there a role for 5-HT1A agonists in the treatment of depression? Biol Psychiatry 2003; 53(3): 193-203.

[92] Depoortere R, Boulay D, Perrault G, *et al.* SSR181507, a dopamine D2 receptor antagonist and 5-HT1A receptor agonist. II: Behavioral profile predictive of an atypical antipsychotic activity. Neuropsychopharmacology 2003; 28(11): 1889-902.

[93] Newman-Tancredi A, Cussac D, Depoortere R. Neuropharmacological profile of bifeprunox: merits and limitations in comparison with other third-generation antipsychotics. Curr Opin Investig Drugs 2007; 8(7): 539-54.

[94] Jones CA, McCreary AC. Serotonergic approaches in the development of novel antipsychotics. Neuropharmacology 2008; 55(6): 1056-65.

[95] Wadenberg ML, Ahlenius S. Antipsychotic-like profile of combined treatment with raclopride and 8-OH-DPAT in the rat: enhancement of antipsychotic-like effects without catalepsy. J Neural Transm Gen Sect 1991; 83(1-2): 43-53.

[96] Wadenberg ML, Hillegaart V. Stimulation of median, but not dorsal, raphe 5-HT1A autoreceptors by the local application of 8-OH-DPAT reverses raclopride-induced catalepsy in the rat. Neuropharmacology 1995; 34(5): 495-9.

[97] Prinssen EP, Kleven MS, Koek W. Interactions between neuroleptics and 5-HT(1A) ligands in preclinical behavioral models for antipsychotic and extrapyramidal effects. Psychopharmacology (Berl) 1999; 144(1): 20-9.

[98] Christoffersen CL, Meltzer LT. Reversal of haloperidol-induced extrapyramidal side effects in cebus monkeys by 8-hydroxy-2-(din-propylamino)tetralin and its enantiomers. Neuropsychopharmacology 1998; 18(5): 399-402.

[99] Bardin L, Auclair A, Kleven MS, *et al*. Pharmacological profiles in rats of novel antipsychotics with combined dopamine D2/serotonin 5-HT1A activity: comparison with typical and atypical conventional antipsychotics. Behav Pharmacol 2007; 18(2): 103-18.

[100] Sumiyoshi T, Matsui M, Nohara S, *et al*. Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am J Psychiatry 2001; 158(10): 1722-5.

[101] Alonso J, Angermeyer MC, Bernert S, *et al*. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 2004; 420 (Suppl): 21-7.

[102] Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008; 358(1): 55-68.

[103] Gordon JA, Hen R. The serotonergic system and anxiety. Neuromolecular Med 2004; 5(1): 27-40.

[104] Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends Pharmacol Sci 1994; 15(7): 220-6.

[105] Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 2007; 12(4): 331-59.

[106] Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology (Berl) 1994; 114(4): 559-65.

[107] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 2006; 7(2): 137-51.

[108] Blier P. The pharmacology of putative early-onset antidepressant strategies. Eur Neuropsychopharmacol 2003; 13(2): 57-66.

[109] Artigas F, Romero L, de Montigny C, Blier P. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci 1996; 19(9): 378-83.

[110] Nestler EJ, Gould E, Manji H, *et al.* Preclinical models: status of basic research in depression. Biol Psychiatry 2002; 52(6): 503-28.

[111] Mathew SJ, Manji HK, Charney DS. Novel drugs and therapeutic targets for severe mood disorders. Neuropsychopharmacology 2008; 33(9): 2080-92.

[112] Schechter LE, Ring RH, Beyer CE, *et al*. Innovative approaches for the development of antidepressant drugs: current and future strategies. NeuroRx 2005; 2(4): 590-611.

[113] Mnie-Filali O, Lambas-Senas L, Zimmer L, Haddjeri N. 5-HT7 receptor antagonists as a new class of antidepressants. Drug News Perspect 2007; 20(10): 613-8.

[114] Lucas G, Rymar VV, Du J, *et al.* Serotonin(4) (5-HT(4)) receptor agonists are putative antidepressants with a rapid onset of action. Neuron 2007; 55(5): 712-25.

[115] Trivedi MH, Thase ME, Osuntokun O, *et al*. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. J Clin Psychiatry 2009; 70(3): 387-96.

[116] Shelton RC, Williamson DJ, Corya SA, *et al.* Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry 2005; 66(10): 1289-97.

[117] Thase ME, Corya SA, Osuntokun O, *et al*. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J Clin Psychiatry 2007; 68 (2): 224-36.

[118] Rapaport MH, Gharabawi GM, Canuso CM, *et al.* Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 2006; 31(11): 2505-13.

[119] Cassano P, Lattanzi L, Soldani F, *et al.* Pramipexole in treatment-resistant depression: an extended follow-up. Depress Anxiety 2004; 20 (3): 131-8.

[120] Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004; 161(3): 564-6.

[121] Worthington JJ, 3rd, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol 2005; 20(1): 9-11.

[122] Sheffrin M, Driscoll HC, Lenze EJ, *et al*. Pilot study of augmentation with aripiprazole for incomplete response in late-life depression: getting to remission. J Clin Psychiatry 2009; 70(2): 208-13.

[123] Berman RM, Marcus RN, Swanink R, *et al*. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007; 68(6): 843-53.

[124] Marcus RN, McQuade RD, Carson WH, *et al.* The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008; 28(2): 156-65.

[125] Arbaizar B, Dierssen-Sotos T, Gomez-Acebo I, Llorca J. Aripiprazole in major depression and mania: meta-analyses of randomized placebo-controlled trials. Gen Hosp Psychiatry 2009; 31(5): 478-83.

[126] Sharp T, Bramwell SR, Grahame-Smith DG. 5-HT1 agonists reduce 5-hydroxytryptamine release in rat hippocampus *in vivo* as determined by brain microdialysis. Br J Pharmacol 1989; 96(2): 283-90.

[127] de Montigny C, Blier P, Chaput Y. Electrophysiologically-identified serotonin receptors in the rat CNS. Effect of antidepressant treatment. Neuropharmacology 1984; 23(12B): 1511-20.

[128] Haddjeri N, Ortemann C, de Montigny C, Blier P. Effect of sustained administration of the 5-HT1A receptor agonist flesinoxan on rat 5-HT neurotransmission. Eur Neuropsychopharmacol 1999; 9(5): 427-40.

[129] Blier P, de Montigny C. Modification of 5-HT neuron properties by sustained administration of the 5-HT1A agonist gepirone: electrophysiological studies in the rat brain. Synapse 1987; 1(5): 470-80.

[130] Celada P, Puig M, Amargos-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. J Psychiatry Neurosci 2004; 29(4): 252-65.

[131] Lucki I. Behavioral studies of serotonin receptor agonists as antidepressant drugs. J Clin Psychiatry 1991; 52 (Suppl): 24-31.

[132] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000; 20(24): 9104-10.

[133] Gould E. Serotonin and hippocampal neurogenesis. Neuropsychopharmacology 1999; 21 (Suppl 2): 46S-51S.

[134] Haddjeri N, Blier P, de Montigny C. Acute and long-term actions of the antidepressant drug mirtazapine on central 5-HT neurotransmission. J Affect Disord 1998; 51(3): 255-66.

[135] Haddjeri N, Blier P, de Montigny C. Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT1A receptors. J Neurosci 1998; 18(23): 10150-6.

[136] Haddjeri N, Szabo ST, de Montigny C, Blier P. Increased tonic activation of rat forebrain 5-HT(1A) receptors by lithium addition to antidepressant treatments. Neuropsychopharmacology 2000; 22(4): 346-56.

[137] Haddjeri N, De Montigny C, Curet O, Blier P. Effect of the reversible monoamine oxidase-A inhibitor befloxatone on the rat 5-hydroxytryptamine neurotransmission. Eur J Pharmacol 1998; 343(2-3): 179-92.

[138] Andrade R, Nicoll RA. Novel anxiolytics discriminate between postsynaptic serotonin receptors mediating different physiological responses on single neurons of the rat hippocampus. Naunyn Schmiedebergs Arch Pharmacol 1987; 336(1): 5-10.

139] Goldberg HL, Finnerty RJ. The comparative efficacy of buspirone and diazepam in the treatment of anxiety. Am J Psychiatry 1979; 136(9): 1184-7.

[140] Bielski RJ, Cunningham L, Horrigan JP, Londborg PD, Smith WT, Weiss K. Gepirone extended-release in the treatment of adult outpatients with major depressive disorder: a double-blind, randomized, placebo-controlled, parallel-group study. J Clin Psychiatry 2008; 69(4): 571-7.

[141] Robinson DS, Rickels K, Feighner J, *et al.* Clinical effects of the 5-HT1A partial agonists in depression: a composite analysis of buspirone in the treatment of depression. J Clin Psychopharmacol 1990; 10 (Suppl 3): 67S-76S.

[142] Stahl SM, Kaiser L, Roeschen J, Keppel Hesselink JM, Orazem J. Effectiveness of ipsapirone, a 5-HT-1A partial agonist, in major depressive disorder: support for the role of 5-HT-1A receptors in the mechanism of action of serotonergic antidepressants. Int J Neuropsychopharmacol 1998; 1(1): 11-18.

[143] Fleurence R, Williamson R, Jing Y, *et al.* A systematic review of augmentation strategies for patients with major depressive disorder. Psychopharmacol Bull 2009; 42(3): 57-90.

[144] Jenkins SW, Robinson DS, Fabre LF, Jr., Andary JJ, Messina ME, Reich LA. Gepirone in the treatment of major depression. J Clin Psychopharmacol 1990; 10 (Suppl 3): 77S-85S.

[145] Sakr A, Andheria M. Pharmacokinetics of buspirone extended-release tablets: a single-dose study. J Clin Pharmacol 2001; 41(7): 783-9.

[146] Wilcox CS, Ferguson JM, Dale JL, Heiser JF. A double-blind trial of low- and high-dose ranges of gepirone-ER compared with placebo in the treatment of depressed outpatients. Psychopharmacol Bull 1996; 32(3): 335-42.

[147] Feiger AD, Heiser JF, Shrivastava RK, *et al.* Gepirone extended-release: new evidence for efficacy in the treatment of major depressive disorder. J Clin Psychiatry 2003; 64(3): 243-9.

[148] Keller MB, Ruwe FJ, Janssens CJ, Sitsen JM, Jokinen R, Janczewski J. Relapse prevention with gepirone ER in outpatients with major depression. J Clin Psychopharmacol 2005; 25(1): 79-84.

[149] Amsterdam JD, Brunswick DJ, Gibertini M. Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. J Psychiatr Res 2004; 38(3): 259-65.

[150] Robinson DS, Sitsen JM, Gibertini M. A review of the efficacy and tolerability of immediate-release and extended-release formulations of gepirone. Clin Ther 2003; 25(6): 1618-33.

[151] Croom KF, Perry CM, Plosker GL. Mirtazapine: a review of its use in major depression and other psychiatric disorders. CNS Drugs 2009; 23(5): 427-52.

[152] Cao BJ, Rodgers RJ. Comparative behavioural profiles of buspirone and its metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) in the murine elevated plus-maze. Neuropharmacology 1997; 36(8): 1089-97.

[153] Bianchi G, Caccia S, Della Vedova F, Garattini S. The alpha 2-adrenoceptor antagonist activity of ipsapirone and gepirone is mediated by their common metabolite 1-(2-pyrimidinyl)-piperazine (PmP). Eur J Pharmacol 1988; 151(3): 365-71.

[154] Judd LL, Akiskal HS, Schettler PJ, *et al.* The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59(6): 530-7.

[155] Schloesser RJ, Chen G, Manji HK. Neurogenesis and neuroenhancement in the pathophysiology and treatment of bipolar disorder. Int Rev Neurobiol 2007; 77: 143-78.

[156] Hirschfeld RM, Keck PE, Jr., Kramer M, *et al.* Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry 2004; 161(6): 1057-65.

[157] Keck PE, Jr., Versiani M, Potkin S, West SA, Giller E, Ice K. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 2003; 160(4): 741-8.

[158] Tohen M, Jacobs TG, Grundy SL, *et al.* Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine HGGW Study Group. Arch Gen Psychiatry 2000; 57(9): 841-9.

[159] Niufan G, Tohen M, Qiuqing A, *et al.* Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. J Affect Disord 2008; 105(1-3): 101-8.

[160] Thase ME, Jonas A, Khan A, *et al.* Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008; 28(1): 13-20.

[161] Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol 2005; 15(1): 75-84.

[162] Keck PE, Jr., McElroy SL. Aripiprazole: a partial dopamine D2 receptor agonist antipsychotic. Expert Opin Investig Drugs 2003; 12(4): 655-62.

[163] Sachs G, Sanchez R, Marcus R, *et al.* Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol 2006; 20(4): 536-46.

[164] Vieta E, Bourin M, Sanchez R, *et al.* Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry 2005; 187: 235-42.

[165] Keck PE, Orsulak PJ, Cutler AJ, *et al.* Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord 2009; 112(1-3): 36-49.

[166] Young AH, Oren DA, Lowy A, *et al.* Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry 2009; 194(1): 40-8.

[167] Keck PE, Jr., Calabrese JR, McQuade RD, *et al.* A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006; 67(4): 626-37.

[168] Keck PE, Jr., Calabrese JR, McIntyre RS, *et al.* Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week,

double-blind study versus placebo. J Clin Psychiatry 2007; 68(10): 1480-91.
[169] Vieta E, T'Joen C, McQuade RD, *et al.* Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. Am J Psychiatry 2008; 165(10): 1316-25.
[170] Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002; 159(7): 1146-54.
[171] Tohen M, Chengappa KN, Suppes T, *et al.* Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002; 59(1): 62-9.
[172] Sachs G, Chengappa KN, Suppes T, *et al*. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2004; 6(3): 213-23.
[173] Jenner P. Functional models of Parkinson's disease: a valuable tool in the development of novel therapies. Ann Neurol 2008; 64 (Suppl 2): S16-29.
[174] Blandini F, Nappi G, Tassorelli C, Martignoni E. Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog Neurobiol 2000; 62(1): 63-88.
[175] Lledo A. Dopamine agonists: the treatment for Parkinson's disease in the XXI century? Parkinsonism Relat Disord 2000; 7(1): 51-58.
[176] Jankovic J. Natural course and limitations of levodopa therapy. Neurology 1993; 43(2): S14-S17.
[177] Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000; 342(20): 1484-91.
[178] Hagan JJ, Middlemiss DN, Sharpe PC, Poste GH. Parkinson's disease: prospects for improved drug therapy. Trends Pharmacol Sci 1997; 18(5): 156-63.
[179] Inzelberg R, Schechtman E, Nisipeanu P. Cabergoline, pramipexole and ropinirole used as monotherapy in early Parkinson's disease: an evidence-based comparison. Drugs Aging 2003; 20(11): 847-55.
[180] Bracco F, Battaglia A, Chouza C, *et al.* The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. CNS Drugs 2004; 18(11): 733-46.
[181] Hauser RA, Bronzova J, Sampaio C, *et al*. Safety and tolerability of pardoprunox, a new partial dopamine agonist, in a randomized, controlled study of patients with advanced parkinson's disease. Eur Neurol 2009; 62(1): 40-8.
[182] Etminan M, Gill S, Samii A. Comparison of the risk of adverse events with pramipexole and ropinirole in patients with Parkinson's disease: a meta-analysis. Drug Saf 2003; 26(6): 439-44.
[183] Lader M. Antiparkinsonian medication and pathological gambling. CNS Drugs 2008; 22(5): 407-16.
[184] Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA 2002; 287(4): 455-63.
[185] Hitzeman N, Rafii F. Dopamine agonists for early Parkinson disease. Am Fam Physician 2009; 80(1): 28-30.
[186] Mengod G, Villaro MT, Landwehrmeyer GB, *et al*. Visualization of dopamine D1, D2 and D3 receptor mRNAs in human and rat brain. Neurochem Int 1992; 20 (Suppl): 33S-43S.
[187] Joyce JN. Dopamine D3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. Pharmacol Ther 2001; 90(2-3): 231-59.
[188] Mercuri NB, Saiardi A, Bonci A, *et al*. Loss of autoreceptor function in dopaminergic neurons from dopamine D2 receptor deficient mice. Neuroscience 1997; 79(2): 323-7.
[189] Bennett JP, Jr., Piercey MF. Pramipexole--a new dopamine agonist for the treatment of Parkinson's disease. J Neurol Sci 1999; 163(1): 25-31.
[190] Lozano AM, Lang AE, Hutchison WD, Dostrovsky JO. New developments in understanding the etiology of Parkinson's disease and in its treatment. Curr Opin Neurobiol 1998; 8(6): 783-90.
[191] Jenner P. Pharmacology of dopamine agonists in the treatment of Parkinson's disease. Neurology 2002; 58 (4 Suppl 1): S1-8.
[192] Ahlenius S, Ericson E, Florvall L, Jimenez P, Hillegaart V, Wijkstrom A. *In vivo* characterization of novel full and partial 2-(4-aminophenyl)-N,N-dipropylethylamine dopamine D(2) receptor agonists. Eur J Pharmacol 2000; 394(2-3): 247-53.
[193] Kannari K, Kurahashi K, Tomiyama M, *et al.* Tandospirone citrate, a selective 5-HT1A agonist, alleviates L-DOPA-induced dyskinesia in patients with Parkinson's disease. No To Shinkei 2002; 54(2): 133-7.
[194] Krosser S, Neugebauer R, Chassard D, Kovar A. Investigation of the impact of sarizotan on the pharmacokinetics of levodopa. Biopharm Drug Dispos 2007; 28(7): 339-47.
[195] Gregoire L, Samadi P, Graham J, Bedard PJ, Bartoszyk GD, Di Paolo T. Low doses of sarizotan reduce dyskinesias and maintain antiparkinsonian efficacy of L-Dopa in parkinsonian monkeys. Parkinsonism Relat Disord 2009; 15(6): 445-52.
[196] Carta M, Carlsson T, Kirik D, Bjorklund A. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain 2007; 130(Pt 7): 1819-33.
[197] Fox SH, Brotchie JM, Lang AE. Non-dopaminergic treatments in development for Parkinson's disease. Lancet Neurol 2008; 7(10): 927-38.
[198] Wang S, Zhang QJ, Liu J, *et al.* Unilateral lesion of the nigrostriatal pathway induces an increase of neuronal firing of the midbrain raphe nuclei 5-HT neurons and a decrease of their response to 5-HT(1A) receptor stimulation in the rat. Neuroscience 2009; 159(2): 850-61.
[199] Frechilla D, Cobreros A, Saldise L, *et al.* Serotonin 5-HT(1A) receptor expression is selectively enhanced in the striosomal compartment of chronic parkinsonian monkeys. Synapse 2001; 39(4): 288-96.
[200] Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ. Tremor in Parkinson's disease and serotonergic dysfunction: an 11C-WAY 100635 PET study. Neurology 2003; 60 (4): 601-5.
[201] Temel Y, Boothman LJ, Blokland A, *et al.* Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. Proc Natl Acad Sci U S A 2007; 104(43): 17087-92.
[202] Cummings JL, Masterman DL. Depression in patients with Parkinson's disease. Int J Geriatr Psychiatry 1999; 14(9): 711-8.
[203] Zesiewicz TA, Hauser RA. Depression in Parkinson's disease. Curr Psychiatry Rep 2002; 4(1): 69-73.

Received: December 17, 2009 Revised: April 04, 2010 Accepted: April 07, 2010