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REVIEW

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Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology

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Dopamine agonists (DA) are therapeutic agents that are commonly used in the treatment of Parkinson's disease (PD). They can reduce undesired motor fluctuations and delay the administration of levodopa therapy. However, this drug family is associated with specific side effects that can significantly diminish the quality of life among PD patients. Some of them impose significant risks for individuals who have a history of cardiovascular diseases, psychosis, and depression, or those older patients who suffer from renal or hepatic insufficiency. Various pharmacokinetic and pharmacodynamic considerations need to be taken into account when administering DA therapy. The goal of this review is to provide a comprehensive, up-to-date overview of DA therapeutic modalities for PD.

INTRODUCTION

Dopamine agonists (DA) are chemical compounds that bind to dopamine receptors in the absence of the endogenous neurotransmitter dopamine. Dopamine receptors are abundantly expressed in many tissues in the body, predominantly in the brain. Two families of dopamine receptors have been identified. They all belong to the G protein-coupled receptor family and exert their physiological effects via a second-messenger system. D1-like family encompasses D_1 and D_5 receptors that are G_S-coupled, while D2-like family includes D_2, D_3 and D_4 receptors that are G_i/G_O coupled [1]. The dopaminergic signaling is implicated in a myriad of physiological functions, including processes such as cognition, memory, pleasure, reward, addiction, pain, fine motor control, modulation of neuroendocrine pathways, and learning [2,3].

It is clinically relevant to have a basic grasp of the dopamine receptor function in order to understand which effects are mediated by dopaminergic signaling [4]. In that regard, the locomotor activity is primarily controlled by D_1, D_2, and D_3 receptors [5]. Moreover, D_1 and D_2 receptors are crucial in learning and memory mechanisms that are mediated by the prefrontal cortex (PFC) and dominantly implicated in reward and reinforcement pathways (D_3 to a lesser degree) [6,7]. It is reasonable to assume that D_2 receptors play an important role in psychotic behaviors since all efficacious antipsychotic drugs have the ability to antagonize D_2 receptors. The dopamine D_3 receptor, located in the limbic area of the brain, mediates drug-seeking behaviors and the future therapeutic efforts are directed toward the development of D_3 receptor ligands that would treat addiction [8]. In a similar fashion, D_4 receptors are implicated in relapse to stimulant use and the selective D_4 antagonists might be used for the treatment of drug relapse [9]. Nonetheless, dopaminergic signaling is important in interactions outside the central nervous system (CNS) – D_2 dopamine receptors in the pituitary gland regulate prolactin secretion and are also present in the glomeruli, zona glomerulosa of the adrenal cortex, renal tubules, and postganglionic sympathetic nerve terminals, while the D_1 family of receptors is present in the juxtaglomerular apparatus and in renal tubules. Consequently, dopamine is implicated in renal and cardiovascular actions such as an increase in myocardial contractility and cardiac output, without changes in heart rate, passive and active vasodilatation,

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†Abbreviations: DA, dopamine agonists; CNS, central nervous system; PD, Parkinson's disease; NMS, non-motor symptoms; L-DOPA, Levodopa; MAO-B, Monoamine oxidase type B; ICD, impulse control disorders; PFC, prefrontal cortex; RLS, restless leg syndrome; ADHD, attention deficit hyperactivity disorder; HRS, hypokinetic-rigid syndrome; CVI, cerebrovascular insult; EMEA, European Medicines Agency; NICE, The National Institute for Health Care and Excellence; EDS, excessive daytime sleepiness; PAP, pulmonary artery pressure

Keywords: dopamine; dopamine agonists; Parkinson's disease; side effects; adverse effects; pharmacology; clinical; patient safety

and increased diuresis/natriuresis [10]. Thus, the biological formation of dopamine receptor heterodimers adds another layer of complexity to the physiological roles of dopaminergic interactions in Parkinson's disease (PD) and such substrates might be viable targets for potential pharmacotherapy in the future [11,12].

There are a number of disorders that occur due to misbalance of dopaminergic signaling. Some of these disorders are dominantly marked by low dopamine levels (hypodopaminergia) or increased dopamine levels (hyperdopaminergia), while many are complex and feature both ends of the spectrum, frequently with pathogenetic implications of other neurotransmitters as well. In some disorders, such as schizophrenia, dopaminergic signaling is complicated and marked by subcortical hyperdopaminergia and prefrontal hypodopaminergia [13]. Dominantly hypodopaminergic disorders include PD or pituitary tumors (prolactinomas). Likewise, restless legs syndrome (RLS) is associated with the hypodopaminergic disturbance in striatal transmission and brain iron insufficiency [14]. Disorders such as attention deficit hyperactivity disorder (ADHD) involve multiple neurotransmitter pathway abnormalities and are marked not just by hypodopaminergia [15]. All of these examples demonstrate that neural transmission pathways in the brain are often perplexing and must be approached from multiple angles.

PD (*paralysis agitans* or *hypokinetic rigid syndrome* — HRS) is a progressive neurodegenerative illness that chiefly affects the motor components of the CNS [16]. This illness affects approximately 1 percent of people ages 60 and older, and is present in 4 percent of the population ages 80 and older [17]. Primary (idiopathic) Parkinsonism occurs due to death and depletion of dopamine-generating cells in the *substantia nigra*, a structure in the basal ganglia within the mesencephalic portion of the CNS. The exact cellular mechanisms of this depletion are not clearly elucidated to this day. Moreover, dopamine neurons in *substantia nigra* are particularly sensitive and can be damaged by conditions such as cerebrovascular insult (CVI), encephalitis, and frequent sports-related concussion injuries. Certain drugs such as neuroleptic antipsychotics (chlorpromazine, haloperidol, etc.) used for the treatment of schizophrenia and psychosis can significantly reduce dopaminergic transmission [18] and cause Parkinson-like symptoms. In a similar fashion, a substantial loss of dopaminergic neurons can be induced by the synthetic drugs such as MPTP or similar neurotoxic substances [19]. Since these causes of a dopaminergic deficit are known, they constitute an entity known as Parkinsonian syndrome or Parkinsonism.

In primary PD, the loss of dopaminergic neurons produces visible motor symptoms such as rigidity of the muscles (hypertonicity), trembling of the limbs when idle (resting tremor), slowness in initiation (akinesia), execution of movement (bradykinesia), and postural instability [16]. Nonmotor symptoms (NMS) that manifest in the form of psychiatric and behavioral deficits such as dementia, cognitive decline, and depression are often present among PD patients and become more dramatic as the disease progresses [20].

Although there is no effective cure for PD, there are a few surgical, pharmacological, and multidisciplinary avenues that can attenuate the effects of the disease and treat it symptomatically. In terms of pharmacological therapy for motor symptoms, three families of drugs are commonly used in clinical practice: Levodopa (L-DOPA), Monoamine oxidase type B (MAO-B) inhibitors, and dopamine agonists [21]. All of these drug classes have a common goal: to restore the equilibrium of dopamine in those regions of the brain where such balance is compromised due to dopaminergic cell loss. Since PD is an illness that has a specific continuity and inherent lows and peaks, treatment often varies depending on the stage of the disease. In addition, these families of drugs utilize different mechanisms while trying to restore dopamine balance.

Side effects are commonly associated with antiparkinsonian pharmacological therapy [22] and can significantly reduce the quality of life of patients suffering from PD. Therefore, it is of cardinal importance to properly recognize and address these side effects when treating a patient with PD. The magnitude of these side effects depends on the treatment regime, type of the drug (or a combination of drugs) used, and psychophysical-genetic constitution of an individual. Due to pharmacodynamic and pharmacokinetic characteristics of these drugs, they can generate an array of side effects. The common ones associated with L-DOPA therapy are involuntary abnormal muscle movements (dyskinesia), an absence of movement (akinesia), nausea, hypotension, muscular rigidity, and psychosis, among others [23]. The pharmacological class of MAO-B inhibitors is associated with sleep disturbances, anxiety, nausea, stomatitis, orthostatic hypotension, and hallucinations [24,25]. Dopamine agonists and side effects of DA therapy, in particular, will be the focus of this review.

CLINICAL USE AND THE ROLE OF DOPAMINE AGONISTS IN A MODERN PD THERAPY

The therapeutic efforts in PD are dominantly symptomatic, while some recent neuroprotective agents that might slow or reverse the natural cause of the disease are under investigation. DA are commonly used agents that exert substantial anti-parkinsonian symptomatic efficacy [26-28]. In the earlier days, DA were first successfully used as an adjunct therapy to established and more potent L-DOPA treatment [29,30]. However, they are now often utilized as a first-line medication for symptomatic treatment of early PD among younger patients (<60 years) since they can delay motor complications, the onset of dyskinesia, and the L-DOPA treatment institution [31-35]. Some authors explicitly argue that the treatment of PD should start with a dopamine agonist [36]. It is important to highlight that DA therapy yields no results in patients who are unresponsive to L-DOPA. In terms of DA, newer extended-release formulations have shown better safety profiles for patients

than immediate-release ones [28]. MAO-B inhibitors such as selegiline or rasagiline may also be used as monotherapy in patients who are in the early stage of the disease and have mild symptoms. L-DOPA is a more potent drug than DAs, however, it is commonly associated with "*on-off*" periods (fluctuating motor responses), dyskinesia, and serious psychiatric side effects [37-39]. Some authors suggest the use of L-DOPA as an initial mode of treatment in all patients with PD (except young), particularly for those with serious cognitiv e or motor impairments that significantly interfere with daily living [40]. Modern therapeutic approaches toward PD often include DAs as the initial monotherapy for the earlier stages of PD, while they are then commonly combined with L-DOPA in later, chronic stages of the disease [41,42]. In this case, doses of L-DOPA should be titrated to the lowest possible amount that is effective to avoid dyskinetic abnormalities and motor fluctuations. Additionally, treatment with L-DOPA should never be stopped abruptly as this might cause malignant hyperthermia (Parkinson hyperpyrexia syndrome).

DA are commonly divided into two groups: ergoline- and non-ergoline-derived agonists. Ergoline agonists are the first generation of DA, derived from ergot, and are associated with specific risks of peritoneal, pulmonary, and cardiac/valvular fibrosis [43,44]. They tend to produce more side effects in a clinical practice due to their "dirty" interactions with receptors other than D_2 family; these include D_1 family, 5-HT and adrenergic receptors [1]. The common drugs in ergoline class are bromocriptine, cabergoline, pergolide, and lisuride. Out of this group, bromocriptine is a cheap drug that is now rarely prescribed, but can be used in combination with L-DOPA in both early and late PD. Cabergoline and pergolide are frequently reserved for the progressive phase of PD, although they can be used as monotherapy in the early phase. However, ergot-derived DAs are generally rarely used these days due to their established risk of valvular and lung fibrosis [48]. A responsible clinician needs to bear in mind that ergoline-derived agonists should not be prescribed to patients who have a positive history of heart, valvular, lung, or abdominal fibrosis. Thus, patients receiving ergoline-derived DA should be monitored with echocardiography before treatment is started and regularly during treatment.

Recent European Medicines Agency (EMEA) guidelines recommend that bromocriptine and dihydroergocryptine should not be prescribed to patients with pre-existing valve problems, while bromocriptine dosage — under all other circumstances — should not exceed more than 30 mg per day [45]. Likewise, the maximum dose of pergolide and cabergoline should be reduced to 3 mg per day. A recent systematic review found that the use of cabergoline and pergolide was associated with a two-fold to seven-fold increase in the incidence of cardiac valve regurgitation [46]. A statistically significant improvement of mitral and tricuspid valve regurgitation score, a sum of rergurgitations, and the thickening of a mitral valve anterior leaflet was found in the long-term echocardiographic study among patients with PD who discontinued their ergot-derived DA therapy [47].

Newer agents, the non-ergoline agonists, are "cleaner" drugs — they bind only to D_2 and D_3 receptors with high affinity, while preserving a modest pharmacodynamic interaction with other receptors [21,49,50]. The National Institute for Health and Care Excellence (NICE) guidelines now give an advantage to non-ergot DA over ergoline class agonists [31]. Likewise, if a dopamine agonist is indicated in the elderly, a non-ergot drug should be preferred [51]. The drugs in this group that are commonly used are pramipexole and ropinirole; these are the most common DA prescribed in the United States (US), while others include rotigotine, piribedil, and apomorphine.

GENERAL INSIGHTS ON DA THERAPY AND OBSERVED SIDE EFFECTS

Therapy with DA often precipitates a wide spectrum of side effects in patients with PD, especially among elderly patients (>65 years) [25]. Such side effects may range from mild and frequent to serious and debilitating [Tables 1A and 1B]. Constipation, nausea, and headaches are commonly associated with DA therapy [52]. Development of excessive daytime sleepiness (EDS) has been associated with DA therapy [53,54], as well as the higher incidence of sleep-disordered breathing (SDB) [55]. Some of the dramatic side effects include hallucinations (both visual, tactile, and auditory), somnolence, peripheral edema, valvular heart disease, fibrosis, and heart failure [33,56-59]. Recently, the association between higher doses of DA therapy and impulse control disorders has been established in a plethora of studies [60-64]. This occurs most likely due to the effect of DA on mesolimbic dopaminergic pathway [65] and/or orbitofrontal cortex [66]. Some studies have shown an increased risk of cancer, particularly liver cancer, in patients who were treated with ergot-derived DA [67]. Likewise, ergot-derived DA are associated with cardiac valve regurgitations and fibrotic changes [68], which should not be overlooked when treating PD patients [69]. Special attention needs to be provided to elderly male patients (>70 years of age) with a history of hypertension when prescribing ergoline DA treatment [70]. Non-ergoline DA are observed to have a better safety profile when it comes to cardiac complications and should be taken into consideration when evaluating the risk-benefit ratio of ergoline derivatives [44,71]. Heart failure has been significantly associated with the use of DA in some recent studies [72,73], although some findings did not support the association between DA therapy and ischemic cardiac complications [74]. Some DA exhibit significant pharmacokinetic features that can affect drug metabolism and clearance, particularly if a patient has renal or hepatic insufficiency [75]. Abrupt and sudden withdrawal of antiparkinsonian drugs is associated with dangerous conditions such as neuroleptic malignant syndrome [76]. It is important to monitor for these side effects when administering DA therapy to elderly patients.

Table 1A. Overview of side effects and pharmacokinetic and pharmacodynamics features of dopamine agonist drugs that are used in the treatment of Parkinson's disease

Drug of Choice [receptor]	Trade Names	Maintenance§ Dose Range	$t_{1/2}$ for elderly Excretion	Interactions/Side effects ±
ERGOLINE CLASS				
Bromocriptine [D2 class primarily] [D2>D3>D4] Not recommended in patients with a positive history of retroperitoneal, pulmonary or cardiac/valvular fibrosis.	Parlodel, Cycloset	Oral, 2.5-40 mg/day It is recommended that maximum daily dose does not exceed 30 mg. (EMEA, 2008)	6-20 hours Bile, 94-98% Renal, 2-6%	**Clinical use:** Useful for early and advanced PD; useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking L-DOPA. Perform regular echocardiographic monitoring and/or pulmonary function tests. **Metabolism:** Hepatic, via CYP3A4, 93 percent first pass metabolism **Common side effects:** constipation, nausea, vomiting, asthenia, dizziness, headache, rhinitis **Serious side effects:** pericardial/pleural effusion, myocardial infarction, heart valve disorder, retroperitoneal and pulmonary fibrosis, gastrointestinal ulcers, hallucinations, psychosis **Notes:** hypersensitivity to ergot alkaloids, should be avoided during breastfeeding and postpartum period, should not be combined with 5-HT receptor agonists (e.g. triptans) due to increased risk of serotonin syndrome
Cabergoline [D2 >> D1] Not recommended in patients with a positive history of retroperitoneal, pulmonary or cardiac/valvular fibrosis.	Caberlin, Dostinex, Cabaser	Oral, 0.125-1 mg 2 x/week It is recommended that maximum daily dose does not exceed 30 mg. (EMEA, 2008)	63-69 hours Fecal, 60% Renal, 22% Unchanged, 4%	**Clinical use:** Useful for early and advanced PD; useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking L-DOPA. Perform regular echocardiographic monitoring and pulmonary function tests. **Metabolism:** Hepatic **Common side effects:** constipation, nausea, dizziness, headache, fatigue **Serious side effects:** congestive heart failure, heart valve disorder, pericardial disease, retroperitoneal fibrosis, pleural effusion, pulmonary fibrosis, pleural fibrosis, peripheral oedema **Notes:** hypersensitivity to ergot derivatives, should not be used in patients with history of cardiac valvulvar disorder, uncontrolled hypertension or pulmonary, retroperitoneal and pericardial fibrotic changes
Lisuride** [D2 class primarily] [5-HT1A, 5-HT2A/C] Not recommended in patients with a positive history of retroperitoneal, pulmonary or cardiac/valvular fibrosis.	Dopergin, Proclacam, Revanil	Oral, 0.2-4.5 mg/day Subcutaneous, 0.035 mg/kg IV, 0.002 mg/kg	1-3 hours 10 hours for metabolites Renal, 50% Bile, 50%	**Clinical use:** Useful for early and advanced PD; useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking L-DOPA. Perform regular echocardiographic monitoring and/or pulmonary function tests. **Metabolism:** Hepatic, via P450 CYP 2D6, 3A4 **Common side effects:** orthostatic hypotension, nausea, headache, tiredness, dizziness, dyskinesia, vertigo, Erytrhomelalgia, Dyspnoea, peripheral edema, sweating **Serious side effects:** Somnolence, sleep disorders, impulse control disorders, cardiac fibrosis, pulmonary fibrosis, pleural fibrosis, pleural effusion, retroperitoneal fibrosis **Notes:** hypersensitivity to ergot derivatives, serious peripheral arterial disorders and coronary insufficiency
Pergolide* [D2 >> D1] [5-HT1, 5-HT2] Not recommended in patients with a positive history of retroperitoneal pulmonary or cardiac/valvular fibrosis.	Permax	Oral, 0.05 mg/day Usual response up to 0.1 mg per day It is recommended that maximum daily dose does not exceed 3 mg. (EMEA, 2008)	27 hours Renal, 50% Fecal, 50%	**Clinical use:** Useful for early and advanced PD; useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking L-DOPA. Perform regular echocardiographic monitoring and/or pulmonary function tests. **Metabolism:** Hepatic, CYP3A4 (major), CYP2D6 (strong) **Common side effects:** constipation, diarrhea, nausea, sedation, orthostatic hypotension, dizziness, tachycardia, dyspnoea, hallucinations, confusion, psychosis, visual disorders **Serious side effects:** cardiac valvulopathy, pleural fibrosis, cardiac failure, impulse control disorders **Notes:** hypersensitivity to ergot derivatives, should not be used in pregnancy and patients with history of fibrotic disorders or cardiac valvulopathy. Withdrawn from US market in 2007 due to increased risk of cardiac fibrosis.

Legend

§ Therapeutic modalities have been designed according to NICE Clinical Guidelines propositions (No.35, 2006)

* withdrawn from the United States' market due to reports claiming association with heart valves damage (2007), still method of treatment in some countries

** discontinued for sale in the United States, used within some European Union countries including the United Kingdom and China

± the common side effects that were reported in at least 10% of cases are displayed in the table

Abbreviations: ER-extended release formula, IR-immediate release formula

Table 1B. Overview of side effects and pharmacokinetic and pharmacodynamics features of dopamine agonist drugs that are used in the treatment of Parkinson's disease

Drug of Choice [receptor]	Trade Names	Maintenance§ Dose Range	$t_{1/2}$ for elderly Excretion	Interactions/Side effects ±
NON-ERGOLINE CLASS				
Pramipexole [D3 > D2, D4] Use for depression subtypes in PD	Mirapex, Mirapexin, Sifrol	Oral, 0.125 mg 3x/day (IR) Oral, 0.375 mg/day (ER)	12 hours Renal, 90% unchanged	**Clinical use:** Useful for the early PD and for patients with PD and motor fluctuations. Can be combined with L-DOPA in late-stage treatment. Watch for the side effects. **Metabolism:** Minimal, < 10% **Common side effects:** orthostatic hypotension (IR), constipation, nausea, asthenia (IR), confusion, dizziness, dyskinesia, extrapyramidal movement, headache, insomnia, hallucinations, edema of the lower extremities **Serious side effects:** hearth failure, Melanoma, Somnolence, psychosis, neuroleptic malignant syndrome, impulse control disorders **Notes:** should decrease dosage in patients with renal insufficiency, use is not recommended in CrCl < 30 mL/min
Ropinirole [D2 >> D3, D4] If experiencing compliance problems, ER formulations may be administered.	Requip, Repreve, Ronirol, Adartrel	Oral, 0.25 mg 3x/day (IR) Oral, 2 mg/day (ER)	6 hours Renal, > 88% Unchanged, <10%	**Clinical use:** Useful for the early PD and for patients with PD and motor fluctuations. Can be combined with L-DOPA in late-stage treatment. Watch for the side-effects. **Metabolism:** Hepatic, via P450 CYP1A2 — can increase ↑ INR prolongation (caution with concomitant use with warfarin) **Side effects (common):** hypotension, orthostatic hypotension, nausea, vomiting, constipation, edema of the lower extremities, impulse control disorders, dizziness, dyskinesia, somnolence, fatigue **Side effects (significant):** sinus node dysfunction, Syncope, sleep attacks, hallucinations
Rotigotine [D1, D2, D3 > D4, D5] Due to transdermal application, potential food or drug interactions within gastrointestinal system are avoided.	Neupro	Transdermal, 2 - 4 mg/day	3 hours initially 5-7 hours (biphasic) Renal, 71% Fecal, 23%	**Clinical use:** Useful for the early PD and for patients with PD and motor fluctuations. Can be combined with L-DOPA in late-stage treatment. Watch for the side effects. Good choice for non-compliant patient that has problems in daily dosing or drug adherence. **Metabolism:** Hepatic – multiple CYP isoenzymes **Common side effects:** orthostatic hypotension, application site reaction, diaphoresis, nausea, vomiting, dizziness, dyskinesia, headache, sleep disturbances, somnolence, fatigue, edema of lower extremities **Serious side effects:** first-degree AV block, syncope, sleep attacks, compulsive behavior, hallucinations, impulse control disorders
Apomorphine [D2, D3, D4 >> D1] Should be used for patients experiencing a sudden, unexpected, and resistant "off" period.	Apokyn, Ixense, Spontane, Uprima	Subcutaneous, 0.2 to 0.6 mL (2-6 mg) for "off" episodes	30-60 minutes	**Clinical use:** Parenteral administration of this drug should be reserved only for those patients experiencing a sudden and resistant "off" period episode. **Metabolism:** Hepatic **Common side effects:** peripheral edema, contusion, injection site reactions, nausea and vomiting, confusion, dizziness, dyskinesia, somnolence, hallucinations, nasal discharge, yawning **Serious side effects:** angina pectoris, cardiac arrest, hypotension, prolonged QT interval, syncope **Notes:** Should be used with concomitant antiemetic — usually domperidone, should be avoided with serotonin 5-HT3 receptor antagonists, possible hypersensitivity, should decrease dosage in patients with renal insufficiency
Piribedil [D2, D3]	Clarium, Pronoran, Trastal, Trivastal	Orally 150-250 mg/day (3-5 divided doses)	Biphasic 1.7 h – first phase 6.9 h – second phase Renal, 68% Bile, 25%	**Clinical use:** Useful for the early PD and for patients with PD and motor fluctuations. Can be combined with L-DOPA in late-stage treatment. Watch for the side effects. **Metabolism:** Hepatic **Common side effects:** nausea, vomiting, confusion, agitation, dizziness, hypotension, orthostatic hypotension, Syncope **Serious side effects:** impulse control disorders, Somnolence **Notes:** Use should be avoided in state of cardiovascular shock, acute phase of myocardial infarction and with concomitant use of antiemetic neuroleptics, piribedil exhibits α2 adrenergic antagonism

Legend

§ Therapeutic modalities have been designed according to NICE Clinical Guidelines propositions (No.35, 2006)

* withdrawn from the United States' market due to reports claiming association with heart valves damage (2007), still method of treatment in some countries

** discontinued for sale in the United States, used within some European Union countries including the United Kingdom, and China

± the common side effects that were reported in at least 10% of cases are displayed in the table

Abbreviations: ER-extended release formula, IR-immediate release formula

ERGOLINE-DERIVED DOPAMINE AGONISTS

Bromocriptine

Bromocriptine is a strong agonist of D2 (D_2>D_3>D_4) class of dopamine receptors, used in adjunct therapy with L-DOPA and as a monotherapy to delay the institution of L-DOPA and minimize fluctuations of motor symptoms [34,77]. Side effects that are commonly associated with bromocriptine are orthostatic hypotension, headache, nausea, and vomiting [78]. Increased dopaminergic transmission via bromocriptine is also associated with psychiatric side effects such as confusion, hallucinations, and delusions [79]. Similarly, presentations of pleuropulmonary fibrosis have been attributed to bromocriptine treatment of PD [80]. The likelihood of valvular regurgitation was increased 3.3-fold in patients that underwent bromocriptine therapy in comparison to controls, and this usually presented in a cumulative dose-dependent manner [81]. Impulse control disorders (ICDs) have also been associated with the administration of bromocriptine [82].

Pergolide

Pergolide pharmacologically acts as an agonist of the D_2 and D_1 dopamine and 5-HT_1 and 5-HT_2 families of serotonin receptors. It has been used as an efficacious and well-tolerated monotherapy for early PD [83]. Restrictive valvular heart disease was present in 33 percent of patients taking pergolide in comparison to controls in a study by Van Camp et al., while a similar study showed that pergolide therapy was associated with an approximately two- to three-fold increased risk of abnormal valves [84,85]. Some studies suggest that this effect might be produced due to high dosage regimens and each 10-mg/kg increase in dose was associated with 1.37 increased odds of developing moderate to severe regurgitation [86,87]. Likewise, pergolide treatment was associated with an increase in pulmonary artery pressure (PAP) [88]. Due to this, pergolide was removed from the US market by the Federal Drug Administration in 2007, although it is still used internationally. Side effects such as increased sedation, somnolence, and daytime sleepiness have also been linked to pergolide use [89].

Cabergoline

Cabergoline is an orally available, long-acting ($t_{1/2}$ = 80 h) D_2 dopamine receptor agonist that also exerts an agonistic effect on D_3, D_4 and 5-HT_2 family of receptors. In addition, this drug antagonizes 5-HT_7 and α2B receptors. Due to its long half-life, cabergoline is conveniently administered in a "once a day" fashion and it significantly delays the onset of motor complications [90]. According to some studies, the likelihood of developing moderate to severe valvular regurgitation was increased from five-fold to seven-fold in patients that were treated with cabergoline, in comparison to placebo or non-ergot DA [88,91,92]. Most of these effects were shown to be dose-dependent [93]. Other side effects that might be associated with cabergoline treatment include nausea, dyspepsia, vomiting, dizziness, postural hypotension, peripheral edema, and increased periods of daytime sleepiness [94].

LISURIDE

Lisuride has been shown as an effective adjunct to L-DOPA in early PD treatment. It is used as an antiparkinsonian treatment option in some countries of the European Union, United Kingdom, and China. The use of lisuride and L-DOPA combined decreased the incidence of dyskinetic and abnormal motor symptoms in the early [95], as well as in the advanced stages of PD [96]. Lisuride is a potent D_2, D_3, and D_4 dopamine receptor agonist, but also acts on 5-HT_{1A} and 5-$HT_{2A/C}$ serotonin receptors [97]. This molecule has a similar pharmacodynamic profile to LSD, but it lacks psychedelic features. It is proposed that agonistic action on 5-HT_{2B} receptors mediates pathological processes within the valves of the heart [98]. Since pharmacodynamic studies showed that lisuride is devoid of this activity, it could be that its use might not induce fibrotic valvulopathy [99,100]. This is an important distinction since a majority of ergot-derived DA are associated with valvular heart diseases. A study that monitored PD patients on a lisuride monotherapy for 12 weeks reported that the most-common side effects were dry mouth, nausea, weakness, postural hypotension, and headache, and that most of these disappeared in three to four days [101].

NON-ERGOLINE DOPAMINE AGONISTS

Pramipexole

Pramipexole exerts a potent agonistic effect on the D_2-family of dopamine receptors with preferential affinity toward D_3 receptors [102]. It produces beneficial effects in early stages of PD, significantly reduces dyskinesia [42,103], and is a valuable option for treating depression associated with bipolar disease [104]. The latter makes it a good option for those patients who develop psychiatric symptoms of depression while suffering from PD [105]. Documented side effects of pramipexole include sleep attacks [106], somnolence (up to 57 percent of patients in one study) [107], and nausea [108]. The risk of peripheral edema was nearly 8 percent in the first year of therapy with pramipexole, and this effect was reinforced if a patient had a history of coronary artery disease [109]. Other noted side effects were constipation, visual/auditory hallucinations, and compulsive eating and weight gain [59,110,111]. A role of pramipexole in causing ICD has been suggested, and a recent study showed that 32 percent of PD patients that were treated with pramipexole as an add-on agonist exhibited ICD symptomatology. This effect is associated with selective D_3 stimulation [63,64,112].

Ropinirole

Ropinirole is a dopamine receptor agonist with the highest affinity for D_2, and then for D_3 and D_4 receptors [113]. It is a viable treatment option for early stages of PD [114]. Similarly to pramipexole, ropinirole has been associated with ICD (present among 25 percent of patients that used it as an add-on agonist) and pathologic impulsive behaviors such as compulsive gambling and hypersexuality [115]. Other side effects of ropinirole include nausea, constipation, dizziness, somnolence, dyskinesia, confusion, hallucinations, and orthostatic hypotension [116-118]. One study found the association of ropinirole with Pisa syndrome (pleurothotonus) [119], but this is not conclusive due to the low level of evidence.

Rotigotine

Rotigotine is a distinct DA in the sense that it is administered via transdermal patch [120]. This feature enables a constant and efficient supply of the drug within 24 hours [121]. It also possesses beneficial antidepressant properties, making it a reasonable treatment option in cases of depressed PD patients [122]. It exhibits a similar safety profile to other non-ergoline DA with nausea (41 percent vs. 17 percent placebo), somnolence (33 percent vs. 20 percent), dizziness (19 percent vs. 13 percent) and dyskinesia as the most reported side effects [123-125]. Application site reactions are common with rotigotine (44 percent vs. 12 percent placebo) [123]. A direct comparison with ropirinole in advanced-stage PD showed that rotigotine had similar efficacy to ropinirole at doses up to 16 mg/24 h, although application site reactions were much higher in the rotigotine group (57.7 percent vs. 18.6 percent) [126].

Piribedil

Piribedil is a piperazine-derived drug that produces an agonistic effect on D_2 and D_3 dopamine receptors and antagonistic effect on α2 receptors [127,128]. Results of the REGAIN study showed that piribedil is effective and safe in early PD therapy [129]. It has been implicated in pathological gambling and impulse control disorders [130,131], as well as a sudden onset of sleep attacks [132]. In terms of circulatory effects, piribedil can produce vasodilatation due to α2 adrenolytic activity, a sympathetic reflex increase of heart rate, plasma renin, and aldosterone levels [133]. Due to all of this, side effects such as orthostatic hypotension and/or syncope are possible [134].

Apomorphine

Apomorphine is a strong non-ergoline D_1 and D_2 class receptor agonist that is mostly used for "off" dyskinetic episodes that occur due to L-DOPA treatment [135]. It can be administered via subcutaneous infusion or intermittent injection [136]. Apomorphine has emetic properties and can also induce hypotension that is not centrally mediated [137]. The common side effects associated with apomorphine are headache, nausea, dizziness [138], postural instability [139], injection site reactions, and psychiatric problems [140]. The introduction of domperidone successfully antagonizes peripheral and cardiovascular dopamine effects of apomorphine [141,142].

ROLE OF THE DOPAMINE AGONISTS IN THE FUTURE

Dopamine agonists have shown a continuous improvement in pharmacodynamic and pharmacokinetic profile over recent years. Potent, but more side effect-prone ergot-derived DA were steadily replaced with second-generation non-ergoline agents. Non-ergoline DA are now preferred since they produce fewer side effects and do not require regular echocardiographic monitoring. One of the disadvantages of these drugs is that they have a shorter half-life and have to be taken multiple times a day, which can seriously affect patient compliance. In this light, transdermal DA — such as rotigotine — that can achieve prolonged effects and provide longer half-lives could be seen as a road to take in the future. In addition, treatment of dyskinesia due to dopaminergic therapy is also underway and some experimental models implicate the importance of NDMA glutamate receptor antagonists in dyskinesia suppression [143]. Further research efforts are necessary to find a dopaminergic agent that will provide selective, long-lasting agonistic effects, with an optimal safety profile.

FUTURE THERAPEUTIC DIRECTIONS IN PD

While the current line of PD treatment is mostly symptomatic, future therapeutic research efforts will certainly shift toward the inhibition or slowing of the neurodegenerative biological mechanisms that are implicated in PD. Drugs that could improve mitochondrial function or increase degradation of defective mitochondria, calcium channel blockers, kinase inhibitors or agents that would prevent misfolding, templating, and transmission of α-synuclein are all potential therapeutic avenues to explore [144]. There is a growing interest in cell therapies that could promote brain repair through novel techniques that include transplantable dopamine neurons derived from pluripotent stem cells or reprogrammed adult somatic cells [145]. Ideally, replenishing dopamine in the basal ganglia would be a permanent solution, and experiments involving gene therapy that would insert the cardinal genes for dopamine production in the striatum are underway. An approach based on a lentiviral vector-based gene therapy named ProSavin has completed an early stage clinical trial [146]. Finally, a recent line of thinking among medical professionals and biomedical scientists in the field is that PD should be perceived as a chronic and progressive inflammatory process in the brain. For this reason, various therapeutic approaches that alter immunologic and cytokine responses in the brain and act in an anti-inflammatory fashion are under investigation. For example, a

selective VIP receptor agonist was found to facilitate immune transformation for dopaminergic neuroprotection in a mouse model of PD [147]. A successful translation of any of these experimental approaches would definitely signify a quantum leap in combating PD, since the spotlight would finally be directed toward the causes and not the consequences of the disease.

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