Review

Receptor Ligands as Helping Hands to L-DOPA in the Treatment of Parkinson’s Disease

Fabio Del Bello, Mario Giannella, Gianfabio Giorgioni *, Alessandro Piergentili and Wilma Quaglia

Scuola di Scienze del Farmaco e dei Prodotti della Salute, Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy; fabio.delbello@unicam.it (F.D.B.); mario.giannella@unicam.it (M.G.); alessandro.piergentili@unicam.it (A.P.); wilma.quaglia@unicam.it (W.Q.)

* Correspondence: gianfabio.giorgioni@unicam.it; Tel.: +39-0737402368

Received: 18 March 2019; Accepted: 6 April 2019; Published: 9 April 2019

Abstract: Levodopa (LD) is the most effective drug in the treatment of Parkinson’s disease (PD). However, although it represents the “gold standard” of PD therapy, LD can cause side effects, including gastrointestinal and cardiovascular symptoms as well as transient elevated liver enzyme levels. Moreover, LD therapy leads to LD-induced dyskinesia (LID), a disabling motor complication that represents a major challenge for the clinical neurologist. Due to the many limitations associated with LD therapeutic use, other dopaminergic and non-dopaminergic drugs are being developed to optimize the treatment response. This review focuses on recent investigations about non-dopaminergic central nervous system (CNS) receptor ligands that have been identified to have therapeutic potential for the treatment of motor and non-motor symptoms of PD. In a different way, such agents may contribute to extending LD response and/or ameliorate LD-induced side effects.

Keywords: Parkinson’s disease; levodopa therapy; levodopa-induced side effects; dopaminergic drugs; non-dopaminergic receptor ligands

1. Introduction

Parkinson’s disease (PD), also known as idiopathic paralysis agitans, is one of the most frequent chronic neurodegenerative diseases worldwide. Although its etiology has not been determined so far, the main pathological characteristic is the decrease of the dopamine (DA) level due to the degeneration of the dopaminergic neurons in the substantia nigra pars compacta [1,2]. This leads to motor (i.e., postural instability, dyskinesias, tremor, and rigidity) and non-motor (i.e., depression, cognitive impairment, pain, hallucinations) symptoms [3–13]. Another pathologically severe aspect is the abnormal formation of protein aggregates inside nerve cells (Lewy bodies), whose primary structural component is the presynaptic neuronal protein α-synuclein. For this reason, PD is classified as synucleopathy. Unfortunately, effective inhibition of progression or the cure for PD is not yet available, while all the available therapies only provide relief for symptoms.

Dopaminergic medications are currently the most effective treatment for both motor and non-motor symptoms, though they are not devoid of limitations and frequently produce undesired side effects. The standard treatment of PD patients consists in the administration of DA in the form of levodopa (LD), a catecholamine produced by the intraneuronal tyrosine hydroxylase [14–19]. Its combination with a peripheral DOPA decarboxylase inhibitor (i.e., carbidopa) increases LD availability in the central nervous system (CNS) and ameliorates the therapeutic profile of LD, prolonging its efficacy [20–22]. An increase in the efficacy of dopaminergic therapy is also obtained by the simultaneous blockade of the DA metabolism with monoaminooxidase B (MAO-B) and/or catechol-O-methyl transferase (COMT) inhibitors [23,24]. Although LD represents the “gold standard” of PD therapy [25], unfortunately,
orally administered LD can cause side effects, including gastrointestinal and cardiovascular symptoms as well as transient elevated liver enzyme levels. Moreover, LD therapy leads to LD-induced dyskinesia (LID) [26], a disabling motor complication that represents a major challenge for the clinical neurologist [27]. Indeed, LID negatively affects the quality of life [28–30] and constitutes a serious obstacle to the management of PD imposing a limit and a reduction of LD dosage, thus restricting treatment efficacy [27].

Numerous therapies are currently being developed to treat the motor and non-motor complications of PD and LID [31]. (See Appendix A for the PubChem CIDs (or Reaxys IDs) of the compounds reported in the review).

Mostly a customized combination of DA agonists and LD formulations is performed. The striatal D1 and D2 receptors are the common binding sites of DA ligands for PD treatment, but lately D3 and D4 subtypes have also become potential targets.

At the best of our knowledge, ten DA agonists are so far available for this disease. They can be listed in ergot DA agonists, including Bromocriptine, Cabergoline, Dihydroergocriptine, Lisuride, and Pergolide and non-ergot DA agonists, including Piribedil, Pramipexole, Ropinirole, Apomorphine, and Rotigotine [32] (Figure 1).

**Ergot DA agonists**

Bromocriptine  
Cabergoline  
Dihydroergocriptine  
Lisuride  
Pergolide

**Non-ergot DA agonists**

Piribedil  
Pramipexole  
Ropinirole  
Apomorphine  
Rotigotine

*Figure 1.* Dopamine (DA) agonists available for Parkinson’s disease (PD) treatment.
Unluckily, DA agonists are not devoid of significant side effects such as hallucinations, hypotension, nausea, vomiting, pathological gambling, compulsive shopping and hypersexuality [33,34]. As a therapeutic example, symptoms of early stage PD may be controlled by the treatment with Pramipexole [35], but after a while a combination with LD is needed to optimize the management of PD symptoms [36]. Thus, DA agonists are typically used either to reduce the dosage of LD or to delay its use (LD sparing) [37], although it has been discussed that dyskinesia evolution is due to disease persistence rather than protracted LD use [38]. Recently, research on dopaminergic targets has produced some new interesting candidates (Figure 2).

**Figure 2.** Emerging dopaminergic ligands as new levodopa (LD) adjuvant candidates.
Among these, Tavapadon (or PF-06649751) is a novel, highly selective D_1/D_5 agonist. A recent paper, reporting about Phase I PD studies, candidates Tavapadon as a novel therapeutic agent for PD with an initial safety, tolerability, and pharmacokinetic profile as well as potential for efficacy. The same report asserts that Phase II clinical trials have been initiated to deeper investigate the potential safety and efficacy of Tavapadon with the aim to determine the dose that can produce relief of symptoms while reducing dependence on LD and, in the meanwhile, avoiding the problems associated with long-term LD administration [39].

Preclinical and clinical studies have indicated the potential utility of D_1 agonists for the treatment of neuropsychiatric disorders. However, these agents are not devoid of limitations. For instance, it has been demonstrated that LID results from increased D_1 receptor-mediated transmission at the level of the direct pathway. Moreover, unlike positive allosteric modulators (PAMs), orthosteric D_1 receptor agonists produce receptor desensitization and an inverted U-shaped dose-response curve [40]. The development of the D_1 PAM DETQ has been reported as a different approach to D_1 receptor activation [41]. Being able to amplify the effects of released endogenous DA in situ, DETQ gives a more physiological response. Its CNS pharmacology strictly reminds that of D_1 agonists, but also shows remarkable differences (i.e., it does not induce stereotypy or desensitization) [41]. The reported behavioral and neurochemical test results suggest a therapeutic utility in neuropsychiatric disorders such as PD [42,43].

It has also been hypothesized that DA receptors in the striatum can form heteromeric complexes. Such an heteromerization leads to changes in the functional and pharmacological properties of receptors compared to their monomorphic subtypes [44,45]. It has been observed a correlation between the expression of D_1–D_3 receptor heteromers and the development of LID [46]. Furthermore, D_3 receptor stimulation can potentiate the D_1 receptor signaling pathway [46,47]. Thus, future D_3 antagonists or partial agonists able to selectively modulate the activity of striatal D_1–D_3 receptor heteromers could be very promising in LID control [48]. Treatment with LD also induces an ectopic expression of D_3 receptors in the DA depleted dorsal striatum, which is associated with dyskinesia [40,46,49]. D_3 receptor involvement in dyskinesia has further been proved by PET studies in humans showing an elevated D_3 receptor binding in patients with dyskinesia [50]. It has been reported that D_3 receptor agonists may produce neuroprotective effects by directly scavenging free radicals, improving the activity of free radical scavenging enzymes, stabilizing the mitochondrial membrane, directly inhibiting neuronal apoptosis. Moreover, being D_3 receptors primarily localized in the midbrain limbic system, which is unrelated to motor function, selective D_3 receptor agonists may have suitable anti-PD activity without significant extrapyramidal side effects [51–55].

The D_3 receptor subtype has also been shown to exhibit biased signaling and desensitization pattern in response to certain agonists, DA included. Such an evidence could significantly contribute to the development of motor and hyperkinetic symptoms in PD and LID, respectively. On the contrary, the closely related D_2 receptors have not demonstrated these D_3 characteristics [40,56]. Thus, it has been demonstrated that the selective D_3 agonist SK609, which does not induce desensitization of D_3 receptors in vivo [57,58], was able to decrease locomotor activity [59,60]. Moreover, it has also been observed a dose dependent efficacy of SK609 in improving motor deficits in PD and ameliorating abnormal involuntary movements (AIMs) in LID using the hemiparkinsonian unilateral lesioned rodent PD model. A combination of SK609 and a low dose of LD induced a motor symptomatic relief without producing AIMs [61].

CJ-1639 is actually one of the most potent and selective D_3 full agonist reported to date that may become one of the newer anti-PD drugs [62,63].

The novel ‘multifunctional’ D_2/D_3 high-affinity compound D-512, endowed with receptor agonist activity together with antioxidant and other neuroprotective features has recently been developed [64, 65]. Compared with Ropinirole, it showed greater peak-dose efficacy and a longer lasting action, thus deserving consideration for clinical investigation.
The novel carbazole-based multifunctional D$_2$/D$_3$ receptor ligands D-636, D-653, and D-656, endowed with high binding affinity and full agonist activity at both receptors [66], have been proved to be highly efficacious in a PD rat model indicating their potential in relieving motor dysfunction in PD. They also exhibited neuroprotective property in an in vitro cellular model of PD. Furthermore, D-636 and D-653 demonstrated potent modulator effect on aggregation and toxicity of α-synuclein protein in vitro. Thus, it has been postulated that multifunctional drugs like D-636, D-653, and D-656 have the potential to alleviate motor dysfunction in PD patients, as well as to modify the disease progression.

**Pardoprunox** (SLV-308), a D$_2$/D$_3$ receptor partial agonist and 5-HT$_{1A}$ receptor full agonist, reached Phase III clinical trials for the treatment of PD. Compared with other dopaminergic agents, it displayed lower propensity to elicit side effects like dyskinesia [67].

Since ligands endowed with such a multitarget profile might be effective in PD pharmacotherapy, novel multitarget compounds based on the N-((6,6-diphenyl-1,4-dioxan-2-yl)methyl)-2-phenoxyethan-1-amine (DDMPA) scaffold were studied. Interestingly, the 3-hydroxy derivative, here named for the first time DDMPA-8, behaved as a partial agonist at D$_2$ and as a potent full agonist at D$_3$ and D$_4$ subtypes. In addition to its potent 5-HT$_{1A}$ receptor agonism, that might be helpful in reducing dyskinetic side effects associated with the dopaminergic stimulation, such a dopaminergic profile makes DDMPA-8 a potential multitarget compound for the treatment of PD. In perspective, its evaluation in PD animal models would shed light on its therapeutic potential [68].

D$_4$ receptors are present within the basal ganglia that represent a key area involved in parkinsonism and, in particular, in dyskinesia [69,70]. During the last years, a renewed interest has emerged around D$_4$ receptors as potential therapeutic target for the treatment of PD, in which D$_4$ antagonists can attenuate LID [71–74]. It has been observed that associating the potent D$_4$ antagonist L-745,870 to LD significantly ameliorates the dyskinesia scenario in LID models. Such a result was quite remarkable since this compound has also demonstrated to be well tolerated in clinical trials. Thus, it could have a rapid development as a new tool for LID treatment. Unfortunately, disappointing results were obtained in the rotarod performance test when co-administered with LD. In fact, L-745,870 reduced the overall LD antiparkinsonian benefit in this model opening only a narrow therapeutic window to its use for the treatment of LIDs [75,76].

The effect of the novel selective D$_4$ antagonist, VU6004461 [77], endowed with high blood–brain barrier penetrability has also been investigated. The clear antidysskinetic effect of both L-745,870 and VU6004461 points to the D$_4$ as a possible future target for the treatment of LID [78]. At present more work is needed, but the use of D$_4$ antagonists for the treatment of LIDs in PD remains a very promising area of research and the development of more highly optimized ligands is still an acceptable challenge [73].

All the results obtained so far are not enough and the rising of the aged population imposes new strategies in PD that may help to manage known limitations of current therapies. Some of the alternative strategies investigated as potential treatment of LID in PD involve non-dopaminergic receptors. To help researchers in such a challenge, this review focuses on recent investigations about non-dopaminergic CNS receptor ligands that have been identified to have therapeutic potential for the treatment of motor and non-motor symptoms of PD. Such agents in different way may contribute to extend LD response and/or ameliorate LD-induced side effects.

2. Serotonin Receptors

The serotonin (5-HT) system has been demonstrated to play a crucial role in the pathogenesis of LID in animal models of PD [79]. Indeed, after advanced dopaminergic cell loss, remaining serotonin neurons can convert exogenous LD to DA and mediate its vesicular storage and release [38,80]. The non-physiological DA release from these neurons might cause DA receptor overstimulation, leading to generation of dyskinesia [81]. Consequently, modulation of 5-HT system has emerged as a promising strategy for LID management. Several studies have shown a reduction of LID induced by targeting different 5-HT receptor (5-HTR) subtypes. 5-HT$_{1A}$R (dorsal raphe nucleus and striatum),
5-HT$_{1A}$R (striatopallidal pathways), and 5-HT$_{2A}$R (substantia nigra pars reticulata and internal segment of the globus pallidus) can modulate DA, GABA, and glutamate release within the basal ganglia to improve motor symptoms of PD and to reduce dyskinesia [82]. 5-HT$_{1A}$R and 5-HT$_{1B}$R agonists, as well as 5-HT$_{2A}$R and 5-HT$_{3}$R antagonists have demonstrated a potential as antidyskinetic agents, while 5-HT$_{4}$ agonists can increase LD-stimulated DA release in CNS.

2.1. 5-HT$_{1A}$Rs

5-HT$_{1A}$R is the most studied of the 5-HT family. Indeed, several preclinical and clinical studies demonstrated that 5-HT$_{1A}$R stimulation (auto- and heteroreceptors) [49,83,84] may reduce dyskinesia through the decrease of DA release [79]. Moreover, 5-HT$_{1A}$R activation may also weaken glutamatergic transmission ameliorating motor symptoms [83].

In a preclinical study, the highly selective 5-HT$_{1A}$ full agonist 8-OH-DPAT and its (R)-(+) eutomer reduced LID, but also worsened motor function in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model [85] (Figure 3).

![Figure 3. 5-HT$_{1A}$R agonists.](image)

Sarizotan, another 5-HT$_{1A}$R full agonist, also endowed with partial D$_2$-like agonist/antagonist profile [86], showed better results as an antidyskinetic agent in a 6-hydroxydopamine (6-OHDA)-lesioned rat model of PD [87]. When evaluated in a Phase II clinical study, at low dose it ameliorated some PD symptoms [88]. However, it failed in attenuating LID compared with placebo in two Phase III studies [89], limiting its therapeutic potential.

The partial 5-HT$_{1A}$R agonists Buspirone and Tandospirone have been shown to possess antidyskinetic properties in humans, but also negatively impacted on parkinsonian symptoms [90,91]. Currently, a Phase III clinical trial is investigating the antidyskinetic potential of Buspirone, which also behaves as a D$_2$-like receptor antagonist [92], on LID (NCT02617017), while a Phase I clinical trial is exploring its potential in combination with the non-selective NMDA antagonist Amantadine (NCT02589340).
Another 5-HT\textsubscript{1A}R partial agonist able to reduce LID in combination with LD in preclinical studies is Eltoprazine [93]. Unlike Buspirone and Tandospirone, this compound also behaves as a 5-HT\textsubscript{1B}R agonist and a 5-HT\textsubscript{2C}R antagonist [94]. In both rodent and monkey models, it abolished LD-mediated motor improvements, suggesting that it may have a narrow therapeutic window [93]. However, the loss of LD efficacy proved to be mitigated by co-administration with 5-hydroxy-tryptophan [95]. When tested in a clinical Phase I/IIa study, Eltoprazine attenuated LID without affecting the antiparkinsonian action of LD [96]. To further validate its efficacy, another Phase II trial is currently ongoing to assess the duration of Eltoprazine’s efficacy in LID management and its effects on motor function (NCT02439125). Preclinical studies have also highlighted the potential efficacy of combining eltoprazine with other compounds able to attenuate LID, such as Amantadine and the selective adenosine A\textsubscript{2A} receptor antagonist Preladenant [93,97,98].

The 5-HT\textsubscript{1A} agonists so far evaluated in clinical trials have shown off-target effects and only partial agonist efficacy at 5-HT\textsubscript{1A}R. In this context, the new highly selective 5-HT\textsubscript{1A}R biased agonists F13714, F15599, and Befiradol (also known as F13640 or NLX112) were recently demonstrated to exhibit exceptionally potent antidyskinetic activity in animal models of PD, while minimally interfering with LD antiparkinsonian effects [99–101]. Biased 5-HT\textsubscript{1A} agonists are selective ligands that act in specific brain regions and preferentially target different 5-HT\textsubscript{1A}R subpopulations [102]. While F13714 and Befiradol preferentially bind presynaptic 5-HT\textsubscript{1A} autoreceptors, F15599 activates postsynaptic 5-HT\textsubscript{1A}Rs [100,103,104]. Befiradol has recently been shown to possess a distinctive in vitro G-protein activation profile in rat brain cell membranes which differs from those of F13714 or F15599 [105]. In particular, it preferentially activate G\textsubscript{ox} proteins over other G-protein subtypes. This compound is currently undergoing clinical development as an antidyskinetic agent (www.parkinsons.org.uk/news/investing-new-treatment-dyskinesia).

2.2. 5-HT\textsubscript{1B}Rs

Although studies with compounds selectively targeting 5-HT\textsubscript{1B}R are limited, the selective 5-HT\textsubscript{1B}R agonist CP94253 demonstrated to attenuate LID in a 6-OHDA-lesioned rat model [81,106] (Figure 4). Interestingly, CP94253 also reduced dyskinesia induced by D\textsubscript{1} receptor agonists at low doses [106]. However, a definitive role of 5-HT\textsubscript{1B}R in LID is difficult to be defined due to very limited clinical studies. Instead, the combination of 5-HT\textsubscript{1B}R and 5-HT\textsubscript{1A}R agonism is more often studied both by monotherapies with mixed actions (e.g., the 5-HT\textsubscript{1A}R/5-HT\textsubscript{1B}R agonist Eltoprazine) or by combined therapies [81]. More recently, the co-administration of the 5-HT\textsubscript{1B} agonist CP94253 with the 5-HT\textsubscript{1A} agonist 8-OH-DPAT and the metabotropic glutamate 5 receptor (mGlu5R) antagonist MTEP elicited a great synergistic antidyskinetic effect without impairment of the antiparkinsonian effects [107].

2.3. 5-HT\textsubscript{2A}Rs

Among 5-HT\textsubscript{2}R subtypes, a potential role in PD and LID has been suggested for 5-HT\textsubscript{2A}R. Pimavanserin (ACP-103), a potent 5-HT\textsubscript{2A}R and less potent 5-HT\textsubscript{2C}R inverse agonist [108], demonstrated to attenuate the expression of LID in cynomolgus monkeys without reducing LD efficacy [109] (Figure 4). This compound has been approved in the United States for the treatment of dopamimetic-induced psychosis in PD patients [110]. However, clinical studies examining this compound against LID have not been reported so far. Evidence in support of Pimavanserin for the management of psychosis in PD patients comes from a Phase III placebo-controlled trial, showing that it was well tolerated and didn’t worse motor function [111].

The highly selective 5-HT\textsubscript{2A} receptor antagonist Pruvanserin (EMD-281,014, LY-2,442,347) demonstrated to reduce the severity of LID and psychosis in a primate PD model, without affecting LD anti-parkinsonian activity [112]. On the contrary, it failed to reduce LD-induced AIMS in 6-OHDA-lesioned rat model, highlighting differences between rodent and primate models of PD [113].

Other evidences of 5-HT\textsubscript{2A}R involvement in LID derive from studies with antipsychotic compounds that are not selective towards such a subtype. For example, in both 6-OHDA-lesioned rat and...
MPTP-lesioned marmoset models, the atypical antipsychotic Clonazepam reduced LID psychosis-like behaviors [114,115]. When tested in humans, Clonazepam successfully reduced both duration and severity of LID symptoms without affecting LD efficacy [116,117]. However, the observation that Clonazepam also displays affinity for other receptors, including 5-HT<sub>2C</sub>, D<sub>2</sub> and D<sub>4</sub>, makes it difficult to evaluate the direct involvement of 5-HT<sub>2A</sub>R.

Quetiapine, another atypical antipsychotic agent targeting 5-HT<sub>2A</sub>R in addition to other systems including adrenergic, muscarinic, histaminergic, and dopaminergic receptors [118,119], effectively reduced LID without interfering with LD efficacy in 6-OHDA-lesioned rat and MPTP-lesioned macaque models [120]. Nevertheless, the results of clinical trials with this compound seem to be conflicting. Indeed, while a clinical study reported that low doses of Quetiapine did not significantly attenuate LID, another study found that it reduced LID with worsening of few motor symptoms [117].

The atypical antipsychotic Aripiprazole is endowed with a multitarget profile, showing antagonism at 5-HT<sub>2A</sub>R and partial agonism at both 5-HT<sub>1A</sub>R and D<sub>2</sub> [122]. In clinical studies it was able to attenuate hallucinations associated with PD, but also reduced LD efficacy in some patients [123]. Moreover, at a very low dose, it provided long-term LID relief [124].

Finally, both Mirtazapine and its analogue Mianserin, antagonists at noradrenergic receptors and 5-HT<sub>2</sub>R/5-HT<sub>3</sub>R [125], demonstrated to reduce LID in NHP models [126,127]. However, Mianserin...
also reduced LD efficacy, limiting its clinical use. In clinical trials mirtazapine was reported to reduce LID without worsening PD symptoms, particularly in patients that were non-responsive to Amantadine [128]. Further clinical studies are in progress.

2.4. 5-HT$_3$Rs

Recently it has been proposed that stimulation of the receptor channel 5-HT$_3$R might affect DA release in striatum. The 5-HT$_3$ antagonist Ondansetron decreased AIMs scores in 6-OHDA-lesioned rat model of PD, suggesting its efficacy in LID. However, it had no effects on motor coordination in rotarod behavioral test [129] (Figure 4).

2.5. 5-HT$_4$Rs

In a recent study, the 5-HT$_4$ agonist Prucalopride, evaluated in a 6-OHDA-lesioned rat model of PD, selectively enhanced LD-stimulated DA release in the substantia nigra pars reticulata and prefrontal cortex (Figure 4). The enterokinetic properties of 5-HT$_4$R agonists suggested their potential use against LD-induced fluctuations in patients with PD [130]. Moreover, since 5-HT$_4$ agonists displayed anxiolytic/antidepressant properties in a mouse corticosterone model [131], Prucalopride may represent an alternative approach to the treatment of anxiety and/or depression in LD-treated patients with PD [132].

The mixed 5-HT$_3$R antagonist/5-HT$_4$R agonist Mosapride proved to be effective in promoting the lower gastrointestinal tract motility and in ameliorating constipation in PD patients [133].

3. Glutamate Receptors

In rodent models of LID, high extracellular levels of glutamate were observed in the striatum and substantia nigra pars reticulata. Molecular imaging studies suggested that similar neurochemical changes of this system are evident in PD patients [134]. Therefore, glutamate receptors represent attractive targets for the treatment of LID. While the first efforts were addressed to antagonize the ionotropic glutamate receptors (iGluRs) N-methyl-D-aspartate (NMDA) and $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) subtypes [135], more recently, metabotropic glutamate receptors (mGluRs) have also been considered as potential targets for PD and LID treatment [136,137].

3.1. iGluRs

Several studies performed in animal models of LID and in post-mortem basal ganglia tissues from dyskinetic PD patients have revealed modifications in the expression and state of phosphorylation of iGluRs, in particular NMDA and AMPA receptors [134]. Therefore, these receptor systems are considered of major importance to the pathophysiology of LID.

3.1.1. NMDA Receptors

Alterations in NMDA receptor trafficking and distribution in the postsynaptic neurons appear to be associated with the extent of DA denervation as well as with the development of LID. However, the exact mechanisms regulating NMDA receptor subcellular trafficking and function in PD and LID are not fully elucidated yet [138,139]. Among the subunits forming the NMDA receptor, GluN2B subunit has attracted considerable interest. Indeed, from radioligand binding studies, performed both in NHP models of LID and dyskinetic PD patients, increased binding densities at GluN2B-containing NMDA receptors in the putamen were observed [140,141]. Furthermore, increased levels of GluN2B phosphorylation have been found in 6-OHDA-lesioned rats after chronic LD treatment [142].

The GluN2B-selective antagonists Ifenprodil and Traxoprodil (CP-101606) were reported to ameliorate parkinsonian symptoms and to reduce LID in rat and NHP models [143–148] (Figure 5).
However, their use has been discouraged in NHP owing to the development of severe side effects, including amnesia and dissociation [143,145,149,150].

Radiprodil, another GluN2B-selective antagonist, in combination with the selective A2A receptor antagonist Tozadenant, significantly improved motor activity both in 6-OHDA-lesioned rats and MPTP-lesioned NHP models, suggesting that the use of such a combination could lead to motor improvement to PD patients, without inducing the motor complications induced by LD therapy [151,152].

Promising results for the treatment of LID were also obtained with the weak non-competitive NMDA receptor antagonists Amantadine and Memantine. Amantadine, historically used as an antiviral agent, showed moderate but significant antidyskinetic efficacy in various clinical trials performed in the last two decades [153–155]. For this reason, it is the only drug with established antidyskinetic activity available in the market [156]. Amantadine treatment proved to reduce the duration of LID and to improve motor disability in PD [157] without major complications [154]. However, there are contrasting results concerning its long-term efficacy [158,159]. A Phase II clinical trial is currently ongoing to study the impact of Amantadine in preventing LID in early PD (NCT01538329). Other Phase II clinical trials are currently underway to evaluate the efficacy of Amantadine, in combination with other classes of drugs (e.g., Buspirone or Eltoprazine, see the section “Serotonin receptors”), in reducing LID in preclinical or clinical trials. Moreover, a recent study has revealed that the combination of a sub-effective dose of Amantadine and the nitric oxide synthase inhibitor 7-Nitroindazole potentiated the effect of reducing LD-induced AIMs in 6-OHDA-lesioned rats when compared to the effect of the drugs alone. This strategy may provide therapeutic benefits to PD patients at lower and thus more tolerable doses [160]. Memantine has also been investigated for its antidyskinetic potential in PD patients, but the results were conflicting. Although Memantine treatment was associated with lower LID scores and reduced daytime duration of dyskinesia, no significant effects on dyskinesia severity were found [161–163].
Other non-competitive NMDA receptor antagonists, including Neu-120 (structure not disclosed), Dizocilpine (MK-810) and Ketamine, displayed potential antidyskinetic effects. Neu-120 is produced by Neurim Pharmaceuticals for the treatment of drug-induced dyskinesias. This compound, that also inhibits MAO-B and GSK-3β, has been subjected to a Phase I/II clinical trial to determine its safety, tolerability, pharmacokinetic and pharmacodynamic profiles in reducing LID in patients with advanced-phase idiopathic PD (NCT00607451). The study has been completed, but the results are not available yet.

Dizocilpine also reduced LD-induced AILs in a rat model of LID, but only at concentrations that worsen parkinsonism [164]. However, when this compound was co-administered with the opioid glycopeptide Lactomorphin (see Figure 17), its pro-parkinsonian activity was suppressed, while a strong antidyskinetic effect remained [165].

Finally, the dissociative anesthetic Ketamine, administered at low sub-anesthetic doses, displayed a long-term effect in reducing LID in a preclinical 6-OHDA-lesioned rat model [166]. This result was confirmed by a clinical trial, in which intravenous infusion of low doses of Ketamine induced a long-lasting therapeutic benefit to reduce LID and depression in PD patients [167].

### 3.1.2. AMPA Receptors

Analogously to NMDA receptors, synaptic localization and phosphorylation of AMPA receptors proved to be altered in animal models of LID and in PD patients [168–171]. Moreover, in MPTP-lesioned monkeys and 6-OHDA-lesioned rats, the pharmacological blockade of AMPA receptors decreased LIDs and enhanced the antiparkinsonian effect of LD [172–174]. Conversely, AMPA receptor agonists triggered dyskinesias [174]. In the light of these findings, treatments with selective AMPA receptor antagonists alone or in combination with selective NMDA receptor antagonists showed beneficial effect in reducing dyskinesia [172].

The anticonvulsants Topiramate and Perampanel are the only AMPA receptor antagonists which have reached clinical trials (Figure 6). Topiramate is a negative modulator of AMPA receptors [175] and a PAM of GABA<sub>A</sub> receptors [176]. It has been reported to improve LID in MPTP-lesioned NHPs [177]. Moreover, in combination with the non-competitive NMDA receptor antagonist Amantadine, Topiramate elicited a synergistic antidyskinetic effect in both rodent and marmoset models of LID at low doses [178]. Despite these positive preclinical experiences, clinical trials have provided conflicting results. In a double-blind trial involving patients with idiopathic PD, Topiramate worsened dyskinesia and was poorly tolerated [179]. No results are so far available for other two Phase II clinical trials evaluating the efficacy of the combination of Amantadine and Topiramate versus Amantadine alone in PD patients with or without dyskinesia (NCT00794313, NCT01789047). Conflicting results were also found in clinical trials with the non-competitive antagonist Perampanel [180–182].

![Figure 6. amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor ligands.](image-url)
In preclinical studies, Talampanel (LY-300164, GYKI 537773), another non-competitive AMPA receptor antagonist, increased the anti-parkinsonian benefits of LD in MPTP-treated monkeys [174], while the competitive AMPA antagonist Tezampanel (LY-293558) was able to reduce wearing-off of LD-induced motor responses in 6-OHDA-lesioned rats [183].

3.2. mGluRs

mGluRs modulate intracellular signaling pathways without blocking the main action of glutamate on excitatory synaptic transmission. For this reason, they may be considered drug targets more convenient than iGluRs. Evidence demonstrated that mGluRs regulate pathophysiologically crucial events related to PD and LID [184,185].

3.2.1. mGlu2/3Rs

mGlu2R and mGlu3R agonists have been proposed to be used in the treatment of PD and LID [134]. In a reserpine-treated model of PD, the mGlu2/3R agonist LY379268 was able to reduce akinesia [186] (Figure 7). However, this result was in contrast with that obtained in the 6-OHDA-lesioned model of PD, in which LY379268 failed to modify the bias towards ipsiversive rotations [186]. It should be considered that discrepancies between results from different PD models may depend on different degrees of DA depletion. LY379268 also failed to produce any amelioration of AIM scores in a rat model of LID [149]. Because of these contrasting effects, the use of mGlu2R and mGlu3R agonists for the treatment of PD and LID may be challenging.

3.2.2. mGlu4Rs

Activation of mGlu4R using PAMs or orthosteric agonists induces antiparkinsonian effects in animal models of PD [187]. The mGlu4R PAMs ADX88178 [188] and Lu AF21934 [189] potentiated the effect of LD without increasing LID in a 6-OHDA-lesioned rat model (Figure 7). The above mentioned PAMs and the orthosteric agonist LSP1-2111 [190], when co-administered with LD, showed LD sparing effect. This makes mGlu4R agonists potentially useful to allow LD to maintain the same benefit on
PD motor symptoms at lower doses. Such an effect would indirectly improve LID. In a more recent study the observation that the stimulation of mGlu4R with the orthosteric agonist LSP1-2111 lacked antidyskinetic and LD-sparing activities while the PAM VU0364770 decreased LID in 6-OHDA-lesioned rats demonstrated that an mGlu4R PAM might be an antidyskinetic agent better than an orthosteric agonist [191].

Recently, novel potent and selective mGlu4R PAMs with improved pharmacokinetic profiles after oral administration have been discovered. Among them, Foliglurax (PXT002331) fully reversed hypokinetic deficits in 6-OHDA-lesioned rats when co-administered with sub-threshold doses of LD [192] and proved to alleviate the motor symptoms of PD and the motor complications induced by LD in primates [193]. Foliglurax is currently being evaluated in Phase IIa trial (NCT03162874) in PD patients affected by LID and wearing-off fluctuations. These results support mGlu4R as a novel and promising therapeutic target for PD and LID.

3.2.3. mGlu5Rs

Several preclinical and clinical studies demonstrated the involvement of mGlu5R in PD and LID. In particular, negative allosteric modulators (NAMs) have proven high efficacy to reverse motor deficits and inhibit LID in both 6-OHDA-lesioned rat and MPTP-lesioned NHP models of PD [184,185].

The NAMs MPEP and MTEP attenuated the effects of LD in inducing involuntary movements in the 6-OHDA-lesioned rat model of LID (Figure 8) [194,195]. Accordingly, MTEP potently inhibited AIMS triggered by the D₁ receptor agonist SKF38393 [107]. MPEP and MTEP also reduced the intensity of LID after acute administration in NHP models of PD [196]. Moreover, MPEP proved to be efficacious after chronic administration without affecting LD efficacy [197]. These results were in line with a previous study, in which the mGlu5R NAM Fenobam reduced LID in both 6-OHDA-lesioned rats and MPTP-lesioned monkeys [198]. Moreover, a combination of Fenobam and Amantadine at sub-threshold doses reduced LID without worsening PD [199], while a combination of MPEP and the adenosine A₂A antagonists MSX-3 and ANR 94 synergistically increased LD-induced turning [200].

![Image of mGlu5R ligands](image-url)

Figure 8. mGlu5R ligands.
Accordingly, in Phase II clinical studies (NCT00582673, NCT00888004, and NCT00986414) the mGlu5R NAM Mavoglurant (AFQ056) demonstrated antidyskinetic efficacy without worsening PD motor symptoms [137,201,202]. The most common adverse events were reported to be dizziness, hallucinations, diarrhea, and insomnia. Unfortunately, Mavoglurant failed to replicate the previous outcome in two subsequent Phase II clinical studies (NCT01491529, NCT01385592), leading to discontinue clinical trials of this compound for the treatment of LID [203]. In another clinical study (NCT01092065), administration of Mavoglurant in patients treated with high doses of LD avoided a worsening of dyskinesia. However, this study was limited by the reduced number of patients, the short treatment duration and the conflicting clinician-rated measures [204].

Among the mGlu5R NAMs, Dipraglurant (ADX48621) showed the most encouraging clinical results. Indeed, in a recent Phase II clinical trial it effectively reduced LID severity including a reduction of dystonia severity and chorea (two major LID components) with no evidence of worsening parkinsonism. Moreover, Dipraglurant demonstrated good safety and tolerability [205], deserving to be further investigated in a larger number of patients to confirm its efficacy in the treatment of LID.

3.2.4. mGlu7Rs and mGlu8Rs

The role played by mGlu7R and mGlu8R in PD and LID need to be elucidated as highly potent and selective ligands have become available only recently and have not been fully pharmacologically characterized yet. Only AMN082, a selective mGlu7R allosteric agonist [206], was shown to have some modest antiparkinsonian effects in reserpine-induced akinesia [207] as well as in haloperidol-induced akinesia animal models [208] (Figure 9).

![AMN082 and DCPG](image)

Figure 9. mGlu7R and mGlu8R ligands.

The mGlu8R agonist DCPG failed to have antiparkinsonian effect in rodent models of PD [207]. However, other studies reported that this compound elicited a reduction of haloperidol-induced catalepsy and reserpine-induced akinesia but only when Haloperidol or Reserpine are administered for a prolonged period of time [209] in 6-OHDA-lesioned rats. This evidence highlighted the need for further studies to understand the mechanisms underlying the antiparkinsonian effects of DCPG.

4. Noradrenergic Receptors

The noradrenergic system plays an important role in the pathophysiology of PD. Noradrenergic neurons in the locus coeruleus [210] undergo degeneration in PD and may even anticipate the death of DA neurons [211–213]. They appear to play a protective role by establishing the extent of nigral degeneration induced by both neurotoxic damage and pathological events underlying PD [212,214,215]. Therefore, the indirect activation of adrenergic pathways by blocking presynaptic α2 adrenergic autoreceptors should prevent the nigrostriatal DA degeneration and subsequent motor deficits in PD.

Moreover, being the noradrenergic system implicated in autonomic function, targeting α2 or β adrenergic receptors (α2-Ars or β-Ars, respectively) appears to have potential to improve symptomatic orthostatic hypertension in PD.
4.1. α2-Ars

Stimulation of α2-Ars overexpressed in striatal GABAergic neurons activates direct basal ganglia pathway and is involved in the generation of LID, justifying the investigation of α2-AR antagonists as antidyskinetic agents [216].

The non-selective α2-AR antagonist Idazoxan was effective in alleviating the expression of AIMs in 6-OHDA-lesioned rats [217] (Figure 10). In a randomized, placebo-controlled pilot study, Idazoxan improved the severity of LIDs without affecting the antiparkinsonian effect of LD [218], but increasing the frequency of cardiovascular side effects.

![Idazoxan, Fipamezole, Propranolol, Salbutamol](image)

**Figure 10.** Noradrenergic receptor ligands.

**Fipamezole**, a more recently developed α2-AR antagonist, has also been shown to extend both the duration and quality of LD action in MPTP-lesioned NHP [219]. A clinical trial with ten PD patients has demonstrated good tolerability and sound antidyskinetic effect [220]. In a Phase II double-blind, placebo-controlled study in US and Indian PD patients Fipamezole did not show any significant antidyskinetic effect. However, the analysis of US subjects revealed that it reduced LIDs in a dose-dependent manner with an acceptable profile of adverse effects [221]. Other clinical trials with Fipamezole have been performed but the results have not been published yet (NCT01149811, NCT01140841, NCT00040209).

4.2. β-ARS

Pharmacological and neuroanatomical evidences support a role for β-ARS as potential therapeutic targets against LID. Indeed, both β1- and β2-ARS are expressed in the striatum [222] and are integral in PD patients [223].

The β2-AR antagonist Propranolol has been reported to reduce LID without affecting LD’s efficacy in several experimental and clinical studies (Figure 10). However, it failed to reduce dyskinesia produced by the D2 receptor agonist SKF81297 or the D3 receptor agonist Quinpirole. Antidyskinetic properties of Propranolol appear to be mediated via attenuation of LD-induced extra-physiological efflux of DA [224]. β blockers might be preferred first-line agents in PD patients who has co-morbid hypertension. Moreover, they are associated with a lower risk of constipation, which is one of the most frequent non-motor symptoms of PD [225]. However, in patients with asthma or chronic obstructive pulmonary disease, β blockers should not be used owing to the risk of bronchospasm [226].

Evidences also support the use of β2-AR agonists in PD therapy. Indeed, from molecular and immunological studies adrenergic stimulation has been suggested to decrease both α-synuclein deposition and release of neurotoxic molecules. In small clinical trials the β2-AR agonist Salbutamol in combination with LD improved parkinsonian symptoms in patients with fluctuating PD. Nevertheless, large randomized controlled trials are lacking [227].

5. Adenosine Receptors

Adenosine is a neuromodulator that regulates responses to DA and other neurotransmitters in areas of the brain that are responsible for motor function as well as learning and memory [228]. While the monotherapy with adenosine receptor antagonists reaches limited efficacy in the treatment of PD, their use as coadjuvants to LD appears to be a promising strategy.
5.1. A₁ Receptors

Adenosine has been reported to antagonize D₁ receptor-mediated transmission through the stimulation of A₁ receptors [229,230], which are widely expressed in the substantia nigra pars reticulate [231]. The selective adenosine A₁ receptor agonist 5′Cl5′d-(±)-ENBA, administered in combination with LD, reduced the development of AIMs, indicating the potential efficacy of A₁ agonists for the treatment of LID and hyperkinetic disorders [232] (Figure 11).

---

**Figure 11.** Adenosine receptor ligands.
5.2. A$_{2A}$ Receptors

A$_{2A}$ receptors are highly expressed and co-localized with D$_2$ and D$_3$ receptors on striatopallidal output neurons in the striatum. Activation of A$_{2A}$ receptors causes the hetero-dimerization with D$_2$ receptors and inhibits indirect basal ganglia pathway from striatum to thalamus [233,234]. As demonstrated by preclinical and clinical studies, A$_{2A}$ receptor antagonists are able to improve motor dysfunctions of PD while reducing side effects such as dyskinesia [235].

Istradefylline (KW6002), one of the first selective A$_{2A}$ antagonists tested in clinics, received marketing approval in Japan in 2013 for the treatment of PD [236] (Figure 11). In preclinical studies, administration of Istradefylline to 6-OHDA-lesioned rats, previously exposed to LD and exhibiting AIMs with each LD intake, did not elicit AIMs. Moreover, Istradefylline didn’t increase AIMs when administered with LD. However, it didn’t enhance the antiparkinsonian action of LD, assessed by the rotarod performance [237]. In the MPTP-lesioned marmoset, administration of Istradefylline reversed parkinsonism similarly to LD, without eliciting dyskinesia [238] and increasing motor activity [239]. When Istradefylline was administered to MPTP-lesioned marmosets previously treated with LD, it enhanced the antiparkinsonian action of the D$_2$ agonist Quinpirole and, at lesser extent, of the D$_1$ agonist SKF-80,723 [240]. The combination of Istradefylline and a low dose of LD caused a reduction of LID after chronic treatment, while maintaining the antiparkinsonian effect [241]. In the MPTP-lesioned macaque, Istradefylline monotherapy reduced parkinsonism [242]. After exposure to LD, it reversed parkinsonian disability without eliciting dyskinesia. Finally, when administered with sub-active dose of LD, Istradefylline did not enhance the antiparkinsonian action and dyskinesia, but specifically alleviated bradykinesia [243,244]. Taken together, these data support the clinical use of Istradefylline as co-adjuvant in PD therapy to manage various LD-induced complications. Istradefylline has been found to improve LD-related motor complications in many clinical trials. Some Phase II and III studies showed significant OFF time reduction in PD patients [245–248]. In contrast, in a large study it failed to demonstrate significant OFF time reduction [249]. Nevertheless, a meta-analysis of all randomized trials concluded that Istradefylline is clinically useful for increasing ON time and reducing OFF time in PD patients with motor fluctuations [250], as supported by a subsequent Phase III trial performed in patients with advanced PD [251]. The findings of an analysis of a post-marketing surveillance study are comparable with previous pre-approval clinical trials in Japan, demonstrating safety and effectiveness of Istradefylline in LD-treated PD patients with the wearing-off phenomenon [252]. Overall, from most of clinical data reported to date, Istradefylline demonstrated to be a well-tolerated and easy to use drug which shows efficacy in advanced PD patients without significantly increasing dyskinesia. This compound might represent a valid adjuvant in LD and other dopaminergic drug therapy to maximize their efficacy and minimize motor fluctuations [253]. Other clinical trials are currently ongoing to confirm the efficacy of Istradefylline in moderate to advanced PD patients (NCT01968031, NCT02610231).

Preladenant (SCH-420,814/MK-3814), another selective competitive A$_{2A}$ receptor antagonist, reversed parkinsonian disability without eliciting dyskinesia in rodent and primate models of PD [254,255]. When added to a low dose of LD, it enhanced its antiparkinsonian effect, without increasing LID [254]. In two Phase II trials evaluating Preladenant in combination with LD in PD patients for 12 or 36 weeks, a significant OFF time reduction was shown [256,257]. On the contrary, in other Phase III and Phase II trials, Preladenant failed to elicit the same effect probably owing to inappropriate study design and execution [258–260].

The A$_{2A}$ antagonist Tozadenant (SYN115) could also alleviate motor fluctuation. Indeed, in a Phase IIa study it elicited faster tapping speed before and during LD infusion compared to placebo [261] and, in a Phase IIb trial it was effective in reducing OFF time [262]. A Phase III study, assessing safety and efficacy of Tozadenant to treat end of dose wearing-off in PD patients using LD is currently ongoing (NCT02453386).

Vipadenant (V2006, BIIB014) is also a selective A$_{2A}$ antagonist which has reached clinical trials for the treatment of PD. This compound reduced OFF time duration and extended ON time in PD
patients, without troublesome dyskinesia. However, 41% of Vipadenant-treated patients experienced adverse effects [263].

Other A2A antagonists that have progressed to Phase I clinical trials include V81444, PBF-509 (structure not disclosed), ST1535 and its metabolites ST4206 and ST3932. V81444 is an A2A antagonist currently under development. In a Phase I study it showed rapid absorption when orally administered, a half-life compatible with twice daily dosing, and minimal urinary excretion [264]. Moreover, a Phase Ib/II study is ongoing (NCT01634568). PBF509 potentiated the activity of LD in reversing parkinsonian motor impairments and inhibited LID in 6-OHDA-lesioned rats [265]. In a Phase I clinical trial (NCT01691924) it showed safety, tolerability and feasibility. ST1535 enhanced LD-induced rotational behavior in 6-OHDA-lesioned rats [266,267] and potentiated the antiparkinsonian action of a sub-active dose of LD in MPTP-lesioned marmosets [268]. A Phase I clinical trial demonstrated that ST1535 was well tolerated [269]. Its metabolites ST4206 and ST3932 showed a similar pharmacological activity and may be considered potentially therapeutic alternatives to ST1535.

5.3. A1/A2A Receptors

The non-specific adenosine receptor antagonist Caffeine has shown antiparkinsonian and neuroprotective effects in animal models of PD [270–272] (Figure 11). A clinical trial demonstrated that Caffeine could reduce the probability of developing dyskinesia [273]. However, in another randomized trial no significant changes in motor features were observed [274]. A Phase III trial to evaluate the efficacy of Caffeine in PD is currently ongoing (NCT01738178).

6. Histamine Receptors

Histamine H2 and H3 receptors are highly expressed in basal ganglia and might be involved in motor activity, thus representing another potential target for the treatment of LID in PD patients [275].

6.1. H2 Receptors

H2 receptors are mainly distributed in basal ganglia, particularly in the striatum. In mouse models the activation of cholinergic interneurons in LID has been demonstrated to be inhibited by blocking H2 histaminergic transmission, providing a strong rationale to reduce LID in PD patients by targeting such receptors [276].

The selective H2 antagonist Famotidine enhanced the antiparkinsonian effects of LD and reduced LID in two mouse models [276] and a primate model of PD [277] (Figure 12). However, a Phase II trial evaluating Famotidine failed to demonstrate efficacy in reducing dyskinesia severity, although this trial used relatively low doses [278].

In PD patients, Nizatidine, another selective H2 antagonist, demonstrated to be efficacious in ameliorating gastroparesis and slow transit constipation [279,280].

6.2. H3 Receptors

The observation that the H3 antagonist Thioperamide potentiated DA agonist-induced locomotor activation suggested a potential benefit of H3 antagonists on motor control in PD patients [281]. Thioperamide was also demonstrated to counteract memory and sleep impairment in a 6-OHDA-lesioned mouse model of PD [282] (Figure 12).

Pitolisant, the only H3 inverse agonist approved for the treatment of narcolepsy with and without cataplexy, is in Phase III clinical trials for the treatment of excessive daytime sleepiness in PD patients (NCT01036139, NCT01066442, NCT00642928).

6.3. H4 Receptors

The activity of microglia, which is regulated by H4 receptors, seems to play a key role in the pathogenesis of PD. Accordingly mRNA expression of H4 receptors proved to be increased in the
basal ganglia of PD patients [283]. In rotenone-induced PD rat model the specific H₄ antagonist JNJ7777120 blocked the microglial activation, reduced apomorphine-induced rotational behavior, prevented decreases in striatal DA levels, providing the first evidence of the efficacy of an H₄ antagonist in PD [284] (Figure 12).

![Histamine receptor ligands](image)

**Figure 12.** Histamine receptor ligands.

7. Cholinergic Receptors

It is well known that DA action is contrasted by acetylcholine (ACh) in striatum and unbalanced signaling between these neurotransmitter systems could alter basal ganglia activity and motor function, as it occurs in PD and LID. Numerous studies show that in PD nigrostriatal damage with severe DA depletion causes abnormal increase in cholinergic interneurons activity that, via strategically positioned nicotinic and muscarinic ACh receptors, promote striatal signaling to attenuate normal movements. Recently, new technology and pharmacological agents have facilitated understanding the role of ACh transmission in PD and LID, thus offering new therapeutic strategies in movement disorders [285–287].

7.1. Muscarinic Receptors

Muscarinic cholinergic antagonists have been considered in the treatment of PD for decades [288]. They are effective in preventing acute dyskinesias, especially in young patients. However, poor subtype selectivity and the occurrence of severe side-effects (confusion, hallucination, dry mouth, memory disturbance, urinary retention) have limited their use [289,290]. Trihexyphenidyl (benzhexol) has been considered one of the most representative compounds within this class. It inhibits the excitability of cholinergic neurons by blocking striatal M₁ receptors. Although it was taken into account for the treatment of PD since 1949, only quite recently it was approved by the FDA for the treatment
of parkinsonian tremor, dyskinetic movements and spastic contractions [291] (Figure 13). When the above-mentioned forms of parkinsonism are treated with LD, Trihexyphenidyl is often used as an adjuvant therapy [291].

![Chemical structures of molecules](image)

**Figure 13.** Muscarinic receptor ligands.

The M₁ receptor antagonist **Benzatropine** also demonstrated to be efficacious for PD tremors [292]. Moreover, the non-subtype selective muscarinic antagonist **Dicyclomine** proved to enhance LD’s antiparkinsonian effects and to significantly attenuate LID in Pitx3-deficient aphakia mice [293].

M₁ muscarinic receptors may also play a role in the modulation of PD non-motor deficits. Indeed, the preferential M₁ antagonist **Telenzepine** demonstrated to improve anxiety-like behavior and social memory recognition in 6-OHDA-lesioned mice, suggesting that dysfunction of the striatal cholinergic system affects emotional and cognitive deficits in mice with reduced DA levels [294].

**Biperiden** is another muscarinic receptor antagonist with high affinity for the M₁ subtype used in the treatment of PD and neuroleptic-induced extrapyramidal motor side effects. Recently, it has also been demonstrated to behave as a weak inhibitor of acetylcholinesterase [295].

Recent studies report that the M₄ PAMs **VU0467154** and **VU0476406** significantly attenuated dyskinetic behaviors in mouse and primate models of LID in PD. These results suggest that activation of M₄ muscarinic receptors, facilitating long-term depotentiation in D₁ medium spiny projection neurons, might represent a novel pharmacological strategy to alleviate LID in PD patients [296].

### 7.2. Nicotinic Agonists

Activation of nicotinic receptors expressed on dopaminergic neurons indirectly affects DA release [297,298]. Moreover, it can also indirectly modulate GABA, serotonin and glutamate release, since nicotinic receptors are also localized on GABAergic, serotonergic and glutamatergic interneurons [299,300]. Preclinical evidence demonstrated that nicotinic receptor ligands reduced LID by up to 60% in different PD animal models [285,287]. However, clinical studies on the involvement of the nicotinic system in LIDs are only emerging [301]. Interestingly, both nicotinic receptor agonists and antagonists similarly demonstrated to reduce LIDs in PD animal models. This can be due to the fact that prolonged exposure to agonist can lead to nicotinic receptor desensitization, ultimately reducing
neurotransmitter release [297,302–305]. Therefore, nicotinic agonists and antagonists induce a similar functional blockade [306].

In addition to providing neuroprotection, **nicotine** also demonstrated to protect against LID in different models of PD [306–317] (Figure 14).

![Nicotine and Mecamylamine](image)

**Figure 14.** Nicotinic receptor ligands.

Interestingly, similar effects were observed with the non-selective nicotinic receptor antagonist **Mecamylamine** [306,310]. In clinical trials Nicotine showed antidyskinetic effect in PD patients after oral treatment [318,319]. Results of a small Phase II trial have never been published (NCT00957918). Preclinical studies have shown that the nicotinic receptor subtypes α7 and β2* (the asterisk indicates the possible presence of other subunits in the receptor complex) are mainly implicated in mediating both neuroprotective and antidyskinetic effects, suggesting that nicotinic subtype selective drugs may be beneficial therapeutic agents for LID management [300,308,320]. The α7 nicotinic receptor agonists **ABT-107** and **ABT-126** significantly reduced LID in PD monkeys without developing tolerance or worsening parkinsonism. ABT-126 was also effective in monkeys with both severe and moderate nigrostriatal damages, suggesting its ability to reduce dyskinesias in early- and later-stage PD [321,322].

Analogously, the selective α7 nicotinic receptor partial agonist **AQW051**, studied in MPTP-lesioned monkeys, reduced LID and extended LD antiparkinsonian response [323]. However, it failed to reduce dyskinesia or parkinsonian severity in idiopathic PD patients [324]. Several β2* nicotinic receptor subtype agonists, including **ABT-089**, **ABT-894**, and **AZD1446**, also demonstrated to significantly reduce LID in most dyskinetic animals without worsening parkinsonism and developing tolerance [325,326]. The extent of LID reduction didn’t increase by co-administration of α7 and β2* nicotinic receptor subtype agonists with respect to the drugs administered alone, suggesting that they act through a common mechanism of action [321]. Overall, the use of compounds selectively targeting β2* or α7 subtype appears to be a good therapeutic approach to alleviate LID. Thus, both classes of drugs may be promising antidyskinetic agents to be tested in clinical trials.

Since attenuated dopaminergic neurodegeneration and motor dysfunction have been observed in hemiparkinsonian α5-KO mice, nicotinic receptors containing the α5 subunit represent potential novel targets in the treatment of PD [327].
8. GABA Receptors

Considering that alterations in GABAergic neurotransmission may contribute to some of the axial symptoms of PD [328], GABA modulation has been proposed as a new strategy for PD treatment [329]. The GABA_A receptor agonist Zolpidem, a PAM with selective affinity for receptors expressing the α1 subunit, improved motor impairments in unilateral 6-OHDA-lesioned rats, suggesting that targeting Zolpidem-sensitive GABA_A receptors may be a novel approach to treat motor symptoms in PD [330] (Figure 15).

![Zolpidem](image1)

Figure 15. GABA receptor ligands.

SAGE-217, another GABA_A receptor PAM, is an orally bioavailable steroidal derivative which has reached a Phase II trial for the treatment of PD as monotherapy or in combination with LD. The results are not available yet (NCT03000569).

9. Neurokinin Receptors

The abnormal stimulation of DA receptors, associated with LID and AIMs, induces up-regulation of FosB expression in dynorphin containing striatal cells where substance P (SP) is co-localized. LD treatment proved to increase SP in the substantia nigra. SP receptor antagonists has been suggested to reduce LID by blocking neurokinin 1 (NK1) receptors. Indeed, in 6-OHDA-lesioned rats the NK1 antagonists Lanepitant (LY303870) and N-acetyl-L-tryptophan demonstrated to ameliorate LID without affecting the therapeutic effect of LD and conserving motor function [331,332] (Figure 16).

![Lanepitant](image2)

Figure 16. Neurokinin receptor ligands.

10. Opioid Receptors

Opioid receptors, especially δ receptor subtype, and the endogenous opioid peptides enkephalin and dynorphin are expressed in basal ganglia and cortex, where the opioid system modulates the activity of spiny projection neurons in motor disorders such as PD [333,334]. The level of opioid peptides demonstrated to be increased in the striatum, thalamus and anterior cingulate cortex [225] in PD animal models and PD patients exhibiting dyskinesia. Therefore, selective agonists and antagonists of opioid receptors have been used to contrast akinesia and LID in PD [335]. Moreover, due to the
well known involvement of opioid in pain, several studies have investigated their potential for the
treatment of pain in PD [288].

**Tapentadol**, a µ opioid receptor agonist with a serotonin/noradrenaline reuptake inhibitor activity,
efficaciously reduced pain and was well tolerated in PD patients [336] (Figure 17).

---

**Figure 17. Opioid receptor ligands.**

The µ opioid receptor antagonists might also be involved in PD therapy. Indeed, in MPTP-lesioned
NHP **Cyprodine** and **ADL5510** (structure not available) reduced LID without affecting the antiparkinsonian
effects of LD [337,338].
A similar effect was induced by the selective δ antagonist Naltrindole, which demonstrated to alleviate LID in MPTP-lesioned marmoset and 6-OHDA-lesioned rats [337,339], while the δ agonist SNC-80 increased locomotor activity in PD animal models [340–342]. On the contrary, the selective κ receptor agonist U50,488 reduced LID in rat and monkey models of PD, although it contrasted the anti-parkinsonian effects of LD [343].

Analogously, the κ agonist and μ antagonist Nalbuphine alleviated LID in an NHP model of PD and decreased the levels of specific dyskinetic molecular markers [344].

Contrasting results were obtained with the non-selective opioid antagonist Naloxone, which reduced LID in 6-OHDA-lesioned rats [114,345], while the same effect was not observed in NHP and PD patients [346,347].

Particularly interesting are the results obtained with DPI-289 a δ Agonist/μ Antagonist (DAMA), which provided anti-parkinsonian action in rodent and NHP models of PD both alone or in combination with LD, without increasing dyskinesia, thus representing an LD-sparing strategy for clinical development [348].

The glycosylated derivative of the opioid peptide Leu-enkephalin Lactomorphin (MMP-2200) [H2N-Tyr-D-Thr-Gly-Phe-Leu-Ser-(O-β-d-lactose)-CONH2] behaved as a mixed δ/μ opioid receptor agonist [349]. This compound showed a modest antiparkinsonian activity, but reduced dyskinesia induced by D2-like receptor agonists [165]. A study evaluating Lactomorphin in combination with the NMDA receptor antagonist MK-801 is reported in the section “glutamate receptors”.

11. Sigma-1 (σ1) Receptors

σ1 Receptor is a type of non-opioid receptor [350] that is down-regulated in the brains of early stage PD patients [351,352]. Recently, the pharmacological stimulation of such a receptor has shown improvement of LID and neurorestorative and protective properties in experimental PD models [352,353].

σ1 Receptor ligands, such as the antagonist BMY-14802 [354], have been reported to be potentially useful for the treatment of LID [355] (Figure 18).

The σ1 receptor agonist Dextromethorphan caused a reduction of dyskinesia by about 30–40%, without affecting the beneficial effect of LD [356]. This compound, that also behaves as a non-competitive NMDA receptor antagonist, as well as a serotonin and norepinephrine reuptake inhibitor is rapidly metabolized by hepatic cytochrome P450 CYP2D6. A Phase IIa clinical trial (NCT01767129) provided preliminary evidence of the efficacy, safety, and tolerability of Dextromethorphan in combination with the potent CYP2D6 inhibitor Quinidine for the treatment of LID in PD patients [357]. However, further studies with a longer treatment duration are needed to validate these early findings.

Pridopidine, a small molecule under development for the treatment of Huntington’s disease [358], produced a significant decrease in LID maintaining the antiparkinsonian benefit of LD in MPTP-lesioned macaques. Although such an effect was associated with full σ1 occupancy, such a mechanism alone is unlikely responsible for the antidyskinetic efficacy of Pridopidine which may be associated with the involvement of non-σ receptors [358].
12. Conclusions

Two hundred years ago James Parkinson described in his work “An essay on the shaking palsy” the characteristic of a CNS chronic degenerative disease lately named with his name (PD) [359]. Despite great progresses over the last 200 years, the therapeutic treatment of this disease, which has become the second most diffused neurodegenerative pathology over the world, still remains an unfulfilled dream and a challenge that scientists have to face. The currently available therapies have demonstrated limited efficacy for the following reasons:

- the causes of such a pathology are mostly unknown;
- the dopaminergic system and other receptors, as well as several enzymatic targets not discussed in this review, mutually affect each other and are deeply altered over the course of the disease (Figure 19);
- the same drug used in PD therapy or for the treatment of co-morbidities may aggravate the progression of different disease symptoms;
- the symptoms are individual and fluctuating during the day;
- frequently divergent results come from the experimental models used in the evaluation of drug candidates.

Figure 19. Pathophysiology of levodopa-induced dyskinesia (Reprinted with permission from Springer Nature: Springer CNS Drugs Pharmacological Strategies for the Management of Levodopa-Induced Dyskinesia in Patients with Parkinson’s Disease, Schaeffer, E.; Pilotto, A.; Berg, D., 2014, doi: 10.1007/s40263-014-0205-z. [360]). ➡️ Physiological activation, ➡➡️ pathological alterations in LD-induced dyskinesia (LID), ➡➡ pathological alterations in LID, ➡ modulatory, ++ increased activation, – decreased activation. \( A_{2A} \) adenosine receptor, \( a_{2a} \) and \( a_{2b} \) noradrenergic receptors, AMPA \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolespropionic acid, \( C_{B1} \) cannabinoid receptor, \( D_1 \) and \( D_2 \) dopaminergic receptors, \( DA \) dopamine, \( DA-autoR \) dopamine autoreceptor, \( DAT \) dopamine transporter, \( GABA \) \( \gamma \)-aminobutyric acid, \( Glu \) glutamate, \( H_3 \) histamine receptor, LID levodopa-induced dyskinesia, \( mGluR \) metabotropic glutamate receptor, \( NA \) noradrenaline, \( nAchR \) nicotinic acetylcholine receptors, \( NMDA \) N-methyl-D-aspartate, \( OP \) opioid receptor.
However, the severity of the disease and its increasing diffusion due to the rising of the aged population prompt to the research of new therapeutic tools both administered alone and/or as LD adjuvant. From this point of view, interesting perspectives are given by the discovery of new ligands targeting different receptor systems, which are discussed in this review.

Moreover, based on the evolution of the traditional concept “one molecule-one target” to the newer “one molecule-one disease” that represents a trend of the modern medicinal chemistry, another helpful “stick of the LD old age” may be represented by multitarget ligands, synergistically able to restore dysfunctions of different system.

Considering the numerous possibilities existing in the field of target-based drug discovery, efficacious therapeutic tools might be hopefully available to PD patients in the future.

**Funding:** This research received no external funding

**Acknowledgments:** This work was supported by grant from the University of Camerino (Fondo di Ateneo per la Ricerca 2018).

**Conflicts of Interest:** The authors declare no conflict of interest.

**Appendix A**

PubChem CIDs (or Reaxys IDs) of the compounds reported in the review

| Compound        | PubChem CID (Reaxys ID) |
|-----------------|-------------------------|
| 5’Cl5’d-(±)-ENBA| 15599147                |
| 8-OH-DPAT       | 1220                    |
| ABT-089         | 178052                  |
| ABT-107         | 11151363                |
| ABT-126         | 24987875                |
| ABT-894         | 10131048                |
| ADX88178        | 46836872                |
| Amantadine      | 2130                    |
| AMN082          | 11698390                |
| ANR 94          | 11805896                |
| Apomorphine     | 6005                    |
| AQW051          | 50914822                |
| Aripiprazole    | 60795                   |
| AZD1446         | 24795080                |
| Befiradol       | 9865384                 |
| Benzatropine    | 1201549                 |
| Biperiden       | 2381                    |
| BMY-14802       | 108046                  |
| Bromocriptine   | 31101                   |
| Buspirone       | 2477                    |
| Cabergoline     | 54746                   |
| Caffeine        | 2519                    |
| CJ-1639         | 53475319                |
| Clozapine       | 135398737               |
| Name                | Code     |
|---------------------|----------|
| CP94253             | 4029677  |
| Cyprodine           | 24758534 |
| D-512               | (26962985) |
| D-636               | (33944059) |
| D-653               | (33944076) |
| D-656               | (33944078) |
| DCPG                | 16062593 |
| DDMPA-8             | (33958274) |
| DETQ                | 117720272 |
| Dextromethorphan    | 5360696  |
| Dicyclomine         | 3042     |
| Dihydroergocriptine | 114948   |
| Dipraglurant        | 44557636 |
| Dizocilpine         | 180081   |
| DPI-289             | (12841869) |
| Eltoprazine         | 65853    |
| F13714              | (8361393) |
| F15599              | 11741361 |
| Famotidine          | 5702160  |
| Fenobam             | 135659063|
| Fipamezole          | 213041   |
| Foliglurax          | 135565465|
| Idazoxan            | 54459    |
| Ifenprodil          | 3689     |
| Istradefylline      | 5311037  |
| JNJ7777120          | 4908365  |
| Ketamine            | 3821     |
| L-745,870           | 5311200  |
| Lactomorphin        | Not Available |
| Lanepeitant         | 3086681  |
| Lisuride            | 28864    |
| LSP1-2111           | 46898088 |
| Lu AF21934          | 66553157 |
| LY379268            | 10197984 |
| Mavoglurant         | 9926832  |
| Mecamylamine        | 4032     |
| Memantine           | 4054     |
| Mianserin           | 4184     |
| Mirtazapine         | 4205     |
| Mosapride           | 119584   |
| Compound                  | Code        |
|--------------------------|-------------|
| MPEP                     | 3025961     |
| MSX-3                    | 10256041    |
| MTEP                     | 9794218     |
| N-acetyl-L-tryptophan    | 700653      |
| Nalbuphine               | 5311304     |
| Naloxone                 | 5284596     |
| Naltrindole              | 5497186     |
| Nicotine                 | 89594       |
| Nizatidine               | 3033637     |
| Ondansetron              | 4595        |
| Perampanel               | 9924495     |
| Pergolide                | 47811       |
| Pimavanserin             | 10071196    |
| Piribedil                | 4850        |
| Pitolisant               | 9948102     |
| Pramipexole              | 119570      |
| Preladenant              | 10117987    |
| Pridopidine              | 9795739     |
| Propranolol              | 4946        |
| Prucalopride             | 3052762     |
| Pruvanserin              | 6433122     |
| Quetiapine               | 5002        |
| Radiprodil               | 10200813    |
| Ropinirole               | 5095        |
| Rotigotine               | 59227       |
| SAGE-217                 | 86294073    |
| Salbutamol               | 2083        |
| Sarizotan                | 6918388     |
| SK609                    | 6486733     |
| SLV-308                  | 6918524     |
| SNC-80                   | 123924      |
| ST1535                   | 9860294     |
| ST3932                   | (20692973)  |
| ST4206                   | 46912314    |
| Talampanel               | 164509      |
| Tandospirone             | 91273       |
| Tapentadol               | 9838022     |
| Tavapadon                | 86764100    |
| Telenzepine              | 5387        |
| Tezampanel               | 127894      |
| Compound          | CAS Number  |
|-------------------|-------------|
| Thioperamide      | 3035905     |
| Topiramate        | 5284627     |
| Tozadenant        | 11618368    |
| Traxoprodil       | 219101      |
| Trihexyphenidyl   | 5572        |
| U50,488           | 3036289     |
| V81444            | 44537963    |
| Vipadenant        | 21874557    |
| VU0364770         | 836002      |
| VU0467154         | (23873237)  |
| VU0476406         | (23873237)  |
| VU6004461         | (29581513)  |
| Zolpidem          | 5732        |

References

1. Apostolova, I.; Taleb, D.S.; Lipp, A.; Galazky, I.; Kupitz, D.; Lange, C.; Makowski, M.R.; Brenner, W.; Amthauer, H.; Plotkin, M.; et al. Utility of Follow-up Dopamine Transporter Spect with 123i-Fp-Cit in the Diagnostic Workup of Patients with Clinically Uncertain Parkinsonian Syndrome. *Clin. Nucl. Med.* 2017, 42, 589–594. [CrossRef]

2. Nido, G.S.; Dolle, C.; Flores, I.; Tuppen, H.A.; Alves, G.; Tysnes, O.B.; Haugarvoll, K.; Tzoulis, C. Ultradeep Mapping of Neuronal Mitochondrial Deletions in Parkinson’s Disease. *Neurobiol. Aging* 2018, 63, 120–127. [CrossRef] [PubMed]

3. Agosti, V.; Vitale, C.; Avella, D.; Rucco, R.; Santangelo, G.; Sorrentino, P.; Varriale, P.; Sorrentino, G. Effects of Global Postural Reeducation on Gait Kinematics in Parkinsonian Patients: A Pilot Randomized Three-Dimensional Motion Analysis Study. *Neurol. Sci.* 2016, 37, 515–522. [CrossRef] [PubMed]

4. Falaki, A.; Huang, X.; Lewis, M.M.; Latash, M.L. Dopaminergic Modulation of Multi-Muscle Synergies in Postural Tasks Performed by Patients with Parkinson’s Disease. *J. Electromyogr. Kinesiol.* 2017, 33, 20–26. [CrossRef] [PubMed]

5. Kataoka, H.; Okada, Y.; Kiriyama, T.; Kita, Y.; Nakamura, J.; Morioka, S.; Shomoto, K.; Ueno, S. Can Postural Instability Respond to Galvanic Vestibular Stimulation in Patients with Parkinson’s Disease? *J. Mov. Disord.* 2016, 9, 40–43. [CrossRef] [PubMed]

6. Ozinga, S.J.; Koop, M.M.; Linder, S.M.; Machado, A.G.; Dey, T.; Alberts, J.L. Three-Dimensional Evaluation of Postural Stability in Parkinson’s Disease with Mobile Technology. *NeuroRehabilitation* 2017, 41, 211–218. [CrossRef] [PubMed]

7. Picconi, B.; Hernandez, L.F.; Obeso, J.A.; Calabresi, P. Motor Complications in Parkinson’s Disease: Striatal Molecular and Electrophysiological Mechanisms of Dyskinesias. *Mov. Disord.* 2018, 33, 867–876. [CrossRef]

8. Silva, K.G.; De Freitas, T.B.; Dona, F.; Gananca, F.F.; Ferraz, H.B.; Torriani-Pasin, C.; Pompeu, J.E. Effects of Virtual Rehabilitation Versus Conventional Physical Therapy on Postural Control, Gait, and Cognition of Patients with Parkinson’s Disease: Study Protocol for a Randomized Controlled Feasibility Trial. *Pilot Feasibility Stud.* 2017, 3, 68. [CrossRef]

9. Wilczyński, J.; Habik, N. The Effect of L-Dopa on Postural Stability in Parkinson’s Disease Patients. *Appl. Sci.* 2019, 9, 409. [CrossRef]

10. Steib, S.; Klamroth, S.; Gassner, H.; Pasluosta, C.; Eskofier, B.; Winkler, J.; Klucken, J.; Pfeifer, K. Perturbation During Treadmill Training Improves Dynamic Balance and Gait in Parkinson’s Disease: A Single-Blind Randomized Controlled Pilot Trial. *Neurorehabil. Neural Repair* 2017, 31, 758–768. [CrossRef]

11. Wilczyński, J.; Pedrycz, A.; Mucha, D.; Ambroz, T.; Mucha, D. Body Posture, Postural Stability, and Metabolic Age in Patients with Parkinson’s Disease. *BioMed Res. Int.* 2017, 2017, 3975417. [CrossRef]
34. Moore, T.J.; Glenmullen, J.; Mattison, D.R. Reports of Pathological Gambling, Hypersexuality, and Compulsive Shopping Associated with Dopamine Receptor Agonist Drugsimpulse Control Disorders and Dopamine Agonsistsimpulse Control Disorders and Dopamine Agonsists. *JAMA Intern. Med.* **2014**, *174*, 1930–1933. [CrossRef] [PubMed]

35. Connolly, B.S.; Lang, A.E. Pharmacological Treatment of Parkinson Disease: A Review. *JAMA* **2014**, *311*, 1670–1683. [CrossRef] [PubMed]

36. Noyes, K.; Dick, A.W.; Holloway, R.G. Pramipexole and Levodopa in Early Parkinson’s Disease. *Pharmacoeconomics* **2005**, *23*, 1257–1270. [CrossRef]

37. Thal, V.; Lo, N.; Robinson, T. Levodopa-Induced Dyskinesia in Parkinson’s Disease: Clinical Features, Pathogenesis, Prevention and Treatment. *Postgrad. Med. J.* **2007**, *83*, 384–388. [CrossRef] [PubMed]

38. Espay, A.J.; Morgante, F.; Merola, A.; Fasano, A.; Marsili, L.; Fox, S.H.; Bezdard, E.; Picconi, B.; Calabresi, P.; Lang, A.E. Levodopa-Induced Dyskinesia in Parkinson Disease: Current and Evolving Concepts. *Ann. Neurol.* **2018**, *84*, 797–811. [CrossRef] [PubMed]

39. Sohur, U.S.; Gray, D.L.; Duvvuri, S.; Zhang, Y.; Thayer, K.; Feng, G. Phase 1 Parkinson’s Disease Studies Show the Dopamine D1/D5 Agonist PF-06649751 Is Safe and Well Tolerated. *Neur. Ther.* **2018**, *7*, 307–319. [CrossRef] [PubMed]

40. Guigoni, C.; Aubert, I.; Li, Q.; Gurevich, V.V.; Benovic, J.L.; Ferry, S.; Mach, U.; Stark, H.; Leriche, L.; Häkansson, K.; et al. Pathogenesis of Levodopa-Induced Dyskinesia: Focus on D1 and D3 Dopamine Receptors. *Parkinsonism Relat. Disord.* **2005**, *11*, S25–S29. [CrossRef]

41. Svensson, K.A.; Heinz, B.A.; Schaus, J.M.; Beck, J.P.; Hao, J.; Krushinski, J.H.; Reinhard, M.R.; Cohen, M.P.; Hellman, S.L.; Getman, B.G.; et al. An Allosteric Potentiator of the Dopamine D1 Receptor Increases Locomotor Activity in Human D1 Knock-in Mice without Causing Stereotypy or Tachyphylaxis. *J. Pharmacol. Exp. Ther.* **2017**, *360*, 117–128. [CrossRef]

42. Bruns, R.F.; Mitchell, S.N.; Wafford, K.A.; Harper, A.J.; Shanks, E.A.; Carter, G.; O’Neill, M.J.; Murray, T.K.; Eastwood, B.J.; Schaus, J.M.; et al. Preclinical Profile of a Dopamine D1 Potentiator Suggests Therapeutic Utility in Neurological and Psychiatric Disorders. *Neuropsychopharmacology* **2018**, *128*, 351–365. [CrossRef]

43. Meltzer, H.Y.; Rajagopal, L.; Matrisianco, F.; Hao, J.; Svensson, K.A.; Huang, M. The Allosteric Dopamine D1 Receptor Potentiator, Detq, Ameliorates Subchronic Phencyclidine-Induced Object Recognition Memory Deficits and Enhances Cortical Acetylcholine Eflux in Male Humanized D1 Receptor Knock-in Mice. *Behav. Brain Res.* **2019**, *361*, 139–150. [CrossRef]

44. Fiorentini, C.; Busi, C.; Gorurso, E.; Gotti, C.; Spano, P.; Missale, C. Reciprocal Regulation of Dopamine D1 and D3 Receptor Function and Trafficking by Heterodimerization. *Mol. Pharmacol.* **2008**, *74*, 59–69. [CrossRef]

45. Marcellino, D.; Ferré, S.; Casadó, V.; Cortés, A.; Le Foll, B.; Mazzola, C.; Drago, F.; Saur, O.; Stark, H.; Soriano, A.; et al. Identification of Dopamine D1–D3 Receptor Heteromers. Indications for a Role of Synergistic D1–D3 Receptor Interactions in the Striatum. *J. Biol. Chem.* **2008**, *283*, 26016–26025. [CrossRef]

46. Solis, O.; Garcia-Montes, J.R.; Gonzalez-Granillo, A.; Xu, M.; Moratalla, R. Dopamine D3 Receptor Modulates L-Dopa-Induced Dyskinesia by Targeting D1 Receptor-Mediated Striatal Signaling. *Cereb. Cortex* **2017**, *27*, 435–446. [CrossRef]

47. Fiorentini, C.; Savoia, P.; Bono, F.; Tallarico, P.; Missale, C. The D3 Dopamine Receptor: From Structural Interactions to Function. *Eur. Neuropsychopharmacol.* **2015**, *25*, 1462–1469. [CrossRef]

48. Solis, O.; Moratalla, R. Dopamine Receptors: Homomeric and Heteromeric Complexes in L-DOPA-Induced Dyskinesia. *J. Neural Transm.* **2018**, *125*, 1187–1194. [CrossRef]

49. Bézard, E.; Ferry, S.; Mach, U.; Léchic, L.; Borod, T.; Gross, C.; Sokoloff, P. Attenuation of Levodopa-Induced Dyskinesia by Normalizing Dopamine D3 Receptor Function. *Nat. Med.* **2003**, *9*, 762–767. [CrossRef]

50. Payer, D.E.; Guttman, M.; Kish, S.J.; Tong, J.; Adams, J.R.; Rusjan, P.; Houle, S.; Futakawa, Y.; Wilson, A.A.; Boileau, I. D3 Dopamine Receptor-Preferring [11C]PHNO PET Imaging in Parkinson Patients with Dyskinesia. *Neurology* **2016**, *86*, 224–230. [CrossRef]

51. Ghosh, B.; Antonio, T.; Zhen, J.; Kharkar, P.; Reith, M.E.A.; Dutta, A.K. Development of (S)-N6-(2-(4-Isoquinolin-1-yl)piperazin-1-yl)ethyl-N6-propyl-4,5,6,7-tetrahydrobenzod-thiazole-2,6-diamine and Its Analogue as a D3 Receptor Preferring Agonist: Potent in Vivo Activity in Parkinson’s Disease Animal Models. *J. Med. Chem.* **2010**, *53*, 1023–1037. [CrossRef]
52. Hiller, C.; Kling, R.C.; Heinemann, F.W.; Meyer, K.; Hübner, H.; Gmeiner, P. Functionally Selective Dopamine D2/D3 Receptor Agonists Comprising an Enyne Moiety. *J. Med. Chem.* 2013, 56, 5130–5141. [CrossRef]

53. Tschammer, N.; Elsner, J.; Goetz, A.; Schuster, S.; Ruberg, M.; Kühn, J.; Thompson, D.; Whistler, J.; Hübner, H.; et al. Highly Potent 5-Aminotetrahydropyrazolopyridines: Enantioselective Dopamine D3 Receptor Binding, Functional Selectivity, and Analysis of Receptor–Ligand Interactions. *J. Med. Chem.* 2011, 54, 2477–2491. [CrossRef]

54. Zhang, H.; Tong, R.; Bai, L.; Shi, J.; Ouyang, L. Emerging Targets and New Small Molecule Therapies in Parkinson’s Disease Treatment. *Bioorg. Med. Chem.* 2016, 24, 1419–1430. [CrossRef]

55. Zhao, Y.; Lu, X.; Yang, C.-y.; Huang, Z.; Fu, W.; Hou, T.; Zhang, J. Computational Modeling toward Understanding Agonist Binding on Dopamine 3. *J. Chem. Inf. Model.* 2010, 50, 1633–1643. [CrossRef] [PubMed]

56. Gil-Mast, S.; Kortagere, S.; Kota, K.; Kuzhikandathil, E.V. An Amino Acid Residue in the Second Extracellular Loop Determines the Agonist-Dependent Tolerance Property of the Human D3 Dopamine Receptor. *ACS Chem. Neurosci.* 2013, 4, 940–951. [CrossRef] [PubMed]

57. Kortagere, S.; Kuzhikandathil, E.V. Novel D3 Dopamine Receptor Agonists to Treat Dyskinesia in Parkinson’s Disease. U.S. Patent WO2012021629 e, 16 February 2012.

58. Westrich, L.; Gil-Mast, S.; Kortagere, S.; Kuzhikandathil, E.V. Development of Tolerance in D3 Dopamine Receptor Signaling Is Accompanied by Distinct Changes in Receptor Conformation. *Biochem. Pharmacol.* 2010, 79, 897–907. [CrossRef] [PubMed]

59. Cote, S.R.; Kuzhikandathil, E.V. In vitro and In vivo Characterization of the Agonist-Dependent D3 Dopamine Receptor Tolerance Property. *Neuropharmacology* 2014, 79, 359–367. [CrossRef]

60. Xu, W.; Wang, X.; Tocker, A.M.; Huang, P.; Reith, M.E.; Liu-Chen, L.Y.; Smith, A.B., 3rd; Kortagere, S. Functional Characterization of a Novel Series of Biased Signaling Dopamine D3 Receptor Agonists. *ACS Chem. Neurosci.* 2017, 8, 486–500. [CrossRef] [PubMed]

61. Simms, S.L.; Huetttner, D.P.; Kortagere, S. In Vivo Characterization of a Novel Dopamine D3 Receptor Agonist to Treat Motor Symptoms of Parkinson’s Disease. *Neuropharmacology* 2016, 100, 106–115. [CrossRef]

62. Chen, J.; Collins, G.T.; Levant, B.; Woods, J.; Deschamps, J.R.; Wang, S. Cj-1639: A Potent and Highly Selective Dopamine D3 Receptor Full Agonist. *ACS Med. Chem. Lett.* 2011, 2, 620–625. [CrossRef]

63. Das, B.; Modii, G.; Dutta, A. Dopamine D3 Agonists in the Treatment of Parkinson’s Disease. *Curr. Top. Med. Chem.* 2015, 15, 908–926. [CrossRef]

64. Lindenbach, D.; Das, B.; Conti, M.M.; Meadows, S.M.; Dutta, A.K.; Bishop, C. D-512, a Novel Dopamine D2/3 Receptor Agonist, Demonstrates Greater Anti-Parkinsonian Efficacy Than Ropinirole in Parkinsonian Rats. *Br. J. Pharmacol.* 2017, 174, 3058–3071. [CrossRef]

65. Santra, S.; Xu, L.; Shah, M.; Johnson, M.; Dutta, A. D-512 and D-440 as Novel Multifunctional Dopamine Agonists: Characterization of Neuroprotection Properties and Evaluation of in vivo Efficacy in a Parkinson’s Disease Animal Model. *ACS Chem. Neurosci.* 2013, 4, 1382–1392. [CrossRef]

66. Elmabruk, A.; Das, B.; Yedlapudi, D.; Xu, L.; Antonio, T.; Reith, M.E.A.; Dutta, A.K. Design, Synthesis, and Pharmacological Characterization of Carbazole Based Dopamine Agonists as Potential Symptomatic and Neuroprotective Therapeutic Agents for Parkinson’s Disease. *ACS Chem. Neurosci.* 2019, 10, 396–411. [CrossRef]

67. Glennon, J.C.; Van Scharrenburg, G.; Ronken, E.; Hesselin, M.B.; Reinders, J.H.; Van Der Neut, M.; Long, S.K.; Feenstra, R.W.; McCreary, A.C. In Vitro Characterization of SLV308 (7-[4-Methyl-1-Piperazinyl]-2(3h)-Benzoxazolone, Monohydrochloride): A Novel Partial Dopamine D2 and D3 Receptor Agonist and Serotonin 5-HT1A Receptor Agonist. *Synapse* 2006, 60, 599–608. [CrossRef]

68. Del Bello, F.; Ambrosini, D.; Bonifazi, A.; Newman, A.H.; Keck, T.M.; Giannella, M.; Giorgioni, G.; Piergentili, A.; Cappellacci, L.; Cilia, A.; et al. Multitarget 1,4-Dioxane Compounds Combining Favorable D2-Like and 5-HT1A Receptor Interactions with Potential for the Treatment of Parkinson’s Disease or Schizophrenia. *ACS Chem. Neurosci.* 2019. [CrossRef]

69. DeLong, M.R. Primate Models of Movement Disorders of Basal Ganglia Origin. *Trends Neurosci.* 1990, 13, 281–285. [CrossRef]

70. Huot, P.; Johnston, T.H.; Koprich, J.B.; Fox, S.H.; Brotchie, J.M. The Pharmacology of L-DOPA-Induced Dyskinesia in Parkinson’s Disease. *Pharmacol. Rev.* 2013, 65, 171–222. [CrossRef]
71. Del Bello, F.; Bonifazi, A.; Giorgioni, G.; Cifani, C.; Micioni Di Bonaventura, M.V.; Petrelli, R.; Piergentili, A.; Fontana, S.; Mammoli, V.; Yano, H.; et al. 1-[3-(4-Butylpiperidin-1-yl)Propyl]-1,2,3,4-Tetrahydropyridine-2-One (77-LH-28-1) as a Model for the Rational Design of a Novel Class of Brain Penetrant Ligands with High Affinity and Selectivity for Dopamine D4 Receptor. *J. Med. Chem.* 2018, 61, 3712–3725. [CrossRef]

72. DeLong, M.R.; Wichmann, T. Circuits and Circuit Disorders of the Basal Ganglia. *Arch. Neurol.* 2007, 64, 20–24. [CrossRef]

73. Lindsley, C.W.; Hopkins, C.R. Return of D4 Dopamine Receptor Antagonists in Drug Discovery. *J. Med. Chem.* 2017, 60, 7233–7243. [CrossRef]

74. Wichmann, T.; DeLong, M.R. Functional Neuroanatomy of the Basal Ganglia in Parkinson’s Disease. *Adv. Neurol.* 2003, 91, 9–18.

75. Huot, P.; Johnston, T.H.; Koprich, J.B.; Aman, A.; Fox, S.H.; Brotchie, J.M. L-745,870 Reduces L-DOPA-Induced Dyskinesia in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Lesioned Macaque Model of Parkinson’s Disease. *J. Pharmacol. Exp. Ther.* 2012, 342, 576–585. [CrossRef]

76. Huot, P.; Johnston, T.H.; Koprich, J.B.; Espinosa, M.C.; Reyes, M.G.; Fox, S.H.; Brotchie, J.M. L-745,870 Reduces the Expression of Abnormal Involuntary Movements in the 6-OHDA-Lesioned Rat. *Behav. Pharmacol.* 2015, 26, 101–108. [CrossRef]

77. Witt, J.O.; McCollum, A.L.; Huffer, M.A.; Huseman, E.D.; Jeffries, D.E.; Temple, K.J.; Plumley, H.C.; Blobaum, A.L.; Lindsley, C.W.; Hopkins, C.R. Synthesis and Characterization of a Series of Chiral Alkoxymethyl Morpholine Analogs as Dopamine Receptor 4 (D4R) Antagonists. *Bioorg. Med. Chem. Lett.* 2016, 26, 2481–2488. [CrossRef]

78. Sebastianutto, I.; Maslava, N.; Hopkins, C.R.; Cenci, M.A. Validation of an Improved Scale for Rating L-Dopa-Induced Dyskinesia in the Mouse and Effects of Specific Dopamine Receptor Antagonists. *Neurobiol. Dis.* 2016, 96, 156–170. [CrossRef]

79. Lanza, K.; Bishop, C. Serotonergic Targets for the Treatment of L-DOPA-Induced Dyskinesia. *J. Neural Transm.* 2018, 125, 1203–1216. [CrossRef]

80. Carta, M.; Tronci, E. Serotonin System Implication in L-Dopa-Induced Dyskinesia: From Animal Models to Clinical Investigations. *Front. Neurol.* 2014, 5, 78. [CrossRef]

81. 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, 1819–1833. [CrossRef]

82. Nicholson, S.L.; Brotchie, J.M. 5-Hydroxytryptamine (5-HT, Serotonin) and Parkinson’s Disease—Opportunities for Novel Therapeutics to Reduce the Problems of Levodopa Therapy. *Eur. J. Neurol.* 2002, 9 (Suppl. 3), 1–6. [CrossRef]

83. Dupre, K.B.; Ostcock, C.Y.; Eskow Jaunarajs, K.L.; Button, T.; Savage, L.M.; Wolf, W.; Bishop, C. Local Modulation of Striatal Glutamate Efflux by Serotonin 1A Receptor Stimulation in Dyskinetic, Hemiparkinsonian Rats. *Exp. Neurol.* 2011, 229, 288–299. [CrossRef]

84. Dupre, K.B.; Ostcock, C.Y.; George, J.A.; Eskow Jaunarajs, K.L.; Hueston, C.M.; Bishop, C. Effects of 5-HT1A Receptor Stimulation on D1 Receptor Agonist-Induced Striatal Activity and Dyskinesia in Hemiparkinsonian Rats. *ACS Chem. Neurosci.* 2013, 4, 747–760. [CrossRef]

85. Iravani, M.M.; Tayarani-Binariz, K.; Chu, W.B.; Jackson, M.J.; Jenner, P. In 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Treated Rats, the Selective 5-Hydroxytryptamine 1a Agonist (R)-(+)8-Ohdpat Inhibits Levodopa-Induced Dyskinesia but Only with Increased Motor Disability. *J. Pharmacol. Exp. Ther.* 2006, 319, 1225–1234. [CrossRef]

86. Bartoszyk, G.D.; Van Amsterdam, C.; Greiner, H.E.; Rautenberg, W.; Russ, H.; Seyfried, C.A. Sarizotan, a Serotonin 5-HT1A Receptor Agonist and Dopamine Receptor Ligand. 1. Neurochemical Profile. *J. Neural Transm. 2004, 111, 113–126. [CrossRef]

87. Bibbiana, F.; Oh, J.D.; Chase, T.N. Serotonin 5-HT1A Agonist Improves Motor Complications in Rodent and Primate Parkinsonian Models. *Neurology* 2001, 57, 1829–1834. [CrossRef]

88. Goetz, C.G.; Damier, P.; Hicking, C.; Laska, E.; Muller, T.; Olanow, C.W.; Rascol, O.; Russ, H. Sarizotan as a Treatment for Dyskinetias in Parkinson’s Disease: A Double-Blind Placebo-Controlled Trial. *Mov. Disord.* 2007, 22, 179–186. [CrossRef]

89. Goetz, C.G.; Laska, E.; Hicking, C.; Damier, P.; Muller, T.; Nutt, J.; Warren Olanow, C.; Rascol, O.; Russ, H. Placebo Influences on Dyskinesia in Parkinson’s Disease. *Mov. Disord.* 2008, 23, 700–707. [CrossRef]
90. Kannari, K.; Kurahashi, K.; Tomiyama, M.; Maeda, T.; Arai, A.; Baba, M.; Suda, T.; Matsunaga, M. Tandospirone Citrate, a Selective 5-HT1A Agonist, Alleviates L-DOPA-Induced Dyskinesia in Patients with Parkinson’s Disease. *No to shinkei = Brain and nerve* 2002, 54, 133–137.

91. Ludwig, C.L.; Weinberger, D.R.; Bruno, G.; Gillespie, M.; Bakker, K.; LeWitt, P.A.; Chase, T.N. Buspirone, Parkinson’s Disease, and the Locus Ceruleus. *Clin. Neuropharmacol.* 1986, 9, 373–378. [CrossRef]

92. Politis, M.; Wu, K.; Loane, C.; Brooks, D.J.; Kiferle, L.; Turkheimer, F.E.; Bain, P.; Mollory, S.; Piccini, P. Serotonergetic Mechanisms Responsible for Levodopa-Induced Dyskinesia in Parkinson’s Disease Patients. *J. Clin. Invest.* 2014, 124, 1340–1349. [CrossRef]

93. Bezard, E.; Tronci, E.; Pioli, E.Y.; Li, Q.; Porras, G.; Bjorklund, A.; Carta, M. Study of the Antidyskinetic Effect of Eltoprazine in Animal Models of Levodopa-Induced Dyskinesia. *Mov. Disord.* 2013, 28, 1088–1096. [CrossRef]

94. Schipper, J.; Tulp, M.T.M.; Sijbesma, H. Neurochemical Profile of Eltoprazine. *Drug Metabol. Drug Interact.* 1990, 8, 85–114. [CrossRef]

95. Tronci, E.; Fidalgo, C.; Stancampiano, R.; Carta, M. Effect of Selective and Non-Selective Serotonin Receptor Activation on L-DOPA-Induced Therapeutic Efficacy and Dyskinesia in Parkinsonian Rats. *Behav. Brain Res.* 2015, 292, 300–304. [CrossRef]

96. Svenningsson, P.; Rosenblad, C.; Af Edholm Arvidsson, K.; Wictorin, K.; Keywood, C.; Shankar, B.; Lowe, D.A.; Bjorklund, A.; Widner, H. Eltoprazine Counteracts L-Dopa-Induced Dyskinesia in Parkinson’s Disease: A Dose-Finding Study. *Brain* 2015, 138, 963–973. [CrossRef]

97. Ko, W.K.D.; Li, Q.; Cheng, L.Y.; Morelli, M.; Carta, M.; Bezard, E. A Preclinical Study on the Combined Effects of Repeated Eltoprazine and Preladenant Treatment for Alleviating L-DOPA-Induced Dyskinesia in Parkinson’s Disease. *Eur. J. Pharmacol.* 2017, 813, 10–16. [CrossRef]

98. Pinna, A.; Ko, W.K.; Costa, G.; Tronci, E.; Fidalgo, C.; Simola, N.; Li, Q.; Tabrizi, M.A.; Bezard, E.; Carta, M.; et al. Antidysskinetic Effect of A2A and 5HT1A/1B Receptor Ligands in Two Animal Models of Parkinson’s Disease. *Mov. Disord.* 2016, 31, 501–511. [CrossRef]

99. Huot, P.; Johnston, T.H.; Fox, S.H.; Newman-Tancredi, A.; Brotchie, J.M. The Highly-Selective 5-HT(1A) Agonist F15599 Reduces L-DOPA-Induced Dyskinesia without Compromising Anti-Parkinsonian Benefits in the MPTP-Lesioned Macaque. *Neuropharmacology* 2015, 97, 306–311. [CrossRef]

100. Iderberg, H.; McCready, A.C.; Varney, M.A.; Cenci, M.A.; Newman-Tancredi, A. Activity of Serotonin 5-HT(1A) Receptor ‘Biased Agonists’ in Rat Models of Parkinson’s Disease and L-DOPA-Induced Dyskinesia. *Neuropharmacology* 2015, 93, 52–67. [CrossRef]

101. Iderberg, H.; McCready, A.C.; Varney, M.A.; Kleven, M.S.; Koek, W.; Bardin, L.; Depoortere, R.; Cenci, M.A.; Newman-Tancredi, A. NLX-112, a Novel 5-HT1A Receptor Agonist for the Treatment of L-DOPA-Induced Dyskinesia: Behavioral and Neurochemical Profile in Rat. *Exp. Neurol.* 2015, 271, 335–350. [CrossRef]

102. Chilmonczyk, Z.; Bojarski, A.J.; Pilc, A.; Sylte, I. Functional Selectivity and Antidepressant Activity of Serotonin 1A Receptor Ligands. *Int. J. Mol. Sci.* 2015, 16, 18478–18506. [CrossRef]

103. Llado-Pelfort, L.; Assie, M.B.; Newman-Tancredi, A.; Artigas, F.; Celada, P. Preferential in Vivo Action of F15599, a Novel 5-HT(1A) Receptor Agonist, at Postsynaptic 5-HT(1A) Receptors. *Br. J. Pharmacol.* 2010, 160, 1929–1940. [CrossRef] [PubMed]

104. Newman-Tancredi, A.; Martel, J.C.; Assie, M.B.; Buritova, J.; Lauressgues, E.; Cosi, C.; Heusler, P.; Bruins Slot, L.; Colpaert, F.C.; Vacher, B.; et al. Signal Transduction and Functional Selectivity of F15599, a Preferential Post-Synaptic 5-HT1A Receptor Agonist. *Br. J. Pharmacol.* 2009, 156, 338–353. [CrossRef] [PubMed]

105. Newman-Tancredi, A.; Varney, M.A.; McCready, A.C. Effects of the Serotonin 5-HT1A Receptor Biased Agonists, F13714 and F15599, on Striatal Neurotransmitter Levels Following L-DOPA Administration in Hemi-Parkinsonian Rats. *Neurochem. Res.* 2018, 43, 1035–1046. [CrossRef] [PubMed]

106. Eskow Jaunaraas, K.L.; Dupre, K.B.; Steiniger, A.; Kloueva, A.; Moore, A.; Kelly, C.; Bishop, C. Serotonin 1B Receptor Stimulation Reduces D1 Receptor Agonist-Induced Dyskinesia. *Neuroreport* 2009, 20, 1265–1269. [CrossRef]

107. Iderberg, H.; Rylander, D.; Bimpisidis, Z.; Cenci, M.A. Modulating mGluR5 and 5-HT1A/1B Receptors to Treat L-Dopa-Induced Dyskinesia: Effects of Combined Treatment and Possible Mechanisms of Action. *Exp. Neurol.* 2013, 250, 116–124. [CrossRef]
108. Roberts, C. ACP-103, a 5-HT2A Receptor Inverse Agonist. *Curr. Opin. Investig. Drugs* 2006, 7, 653–660. [PubMed]

109. Vanover, K.E.; Betz, A.J.; Weber, S.M.; Bibbiani, F.; Kielaita, A.; Weiner, D.M.; Davis, R.E.; Chase, T.N.; Salamone, J.D. A 5-HT2A Receptor Inverse Agonist, ACP-103, Reduces Tremor in a Rat Model and Levodopa-Induced Dyskinesias in a Monkey Model. *Pharmacol. Biochem. Behav.* 2008, 90, 540–544. [CrossRef]

110. Stahl, S.M. Mechanism of Action of Pimavanserin in Parkinson’s Disease Psychosis: Targeting Serotonin 5HT2A and 5HT2C Receptors. *CNS Spectr.* 2016, 21, 271–275. [CrossRef]

111. Cummings, J.; Isaacson, S.; Mills, R.; Williams, H.; Chi-Burris, K.; Corbett, A.; Dhall, R.; Ballard, C. The Highly Selective 5-HT2A Antagonist EMD-281,014 Reduces Dyskinesia and Psychosis in the L-Dopa-Treated Parkinsonian Marmoset. *Neuropharmacology* 2018, 139, 61–67. [CrossRef]

112. Hamadjida, A.; Nuara, S.G.; Bedard, D.; Gaudette, F.; Beaudry, F.; Gourdon, J.C.; Huot, P. The Effect of Mianserin on the Severity of Psychosis and Dyskinesia in a Rat Model of Parkinson’s Disease. *Eur. J. Neurosci.* 2002, 15, 120–132. [CrossRef]

113. Visanji, N.P.; Gomez-Ramirez, J.; Johnston, T.H.; Pires, D.; Voon, V.; Brotchie, J.M.; Fox, S.H. Pharmacological Characterization of Psychosis-Like Behavior in the MPTP-Lesioned Nonhuman Primate Model of Parkinson’s Disease. *Mov. Disord.* 2006, 21, 1879–1891. [CrossRef]

114. Lundblad, M.; Andersson, M.; Winkler, C.; Kirik, D.; Wierup, N.; Cenci, M.A. Pharmacological Validation of Behavioural Measures of Akinesia and Dyskinesia in a Rat Model of Parkinson’s Disease. *Eur. J. Neurosci.* 2004, 27, 153–156. [CrossRef]

115. Gefvert, O.; Bergstrom, M.; Langstrom, B.; Lindstrom, L.; Yates, R. Time Course of Central Nervous Dopamine-D2 and 5-HT2 Receptor Blockade and Plasma Drug Concentrations after Discontinuation of Quetiapine (Seroquel) in Patients with Schizophrenia. *Psychopharmacology* 1998, 135, 119–126. [CrossRef]

116. Goetz, C.G.; Factor, S.A.; Ondo, W.G.; Wojcieszek, J.; Carson, W.H.; Marcus, R.N. Pharmacodynamic Validation of Quetiapine (Seroquel) in Patients with Schizophrenia. *Psychopharmacology* 2002, 164, 533–540. [CrossRef]

117. Oh, J.D.; Bibbiani, F.; Chase, T.N. Quetiapine Attenuates Levodopa-Induced Motor Complications in Rodent and Primate Parkinsonian Models. *Exp. Neurol.* 2006, 2078–2081. [CrossRef] [PubMed]

118. Katzenschlager, R.; Manson, A.J.; Evans, A.; Watt, H.; Lees, A.J. Low Dose Quetiapine for Drug Induced Dyskinesias in Parkinson’s Disease: A Double Blind Cross over Study. *J. Neurol. Neurosurg. Psychiatry* 2004, 75, 295–297.

119. Grunder, G.; Kungel, M.; Ebrecht, M.; Gorocs, T.; Modell, S. Aripiprazole: Pharmacodynamics of a Dopamine Partial Agonist for the Treatment of Schizophrenia. *Pharmacopsychiatry* 2006, 39 (Suppl. 1), S21–25. [CrossRef]

120. Friedman, J.H.; Berman, R.M.; Goetz, C.G.; Factor, S.A.; Ondo, W.G.; Wojcieszek, J.; Carson, W.H.; Marcus, R.N. Open-Label Flexible-Dose Pilot Study to Evaluate the Safety and Tolerability of Aripiprazole in Patients with Psychosis Associated with Parkinson’s Disease. *Mov. Disord.* 2006, 21, 2078–2081. [CrossRef] [PubMed]

121. Katzenschlager, R.; Manson, A.J.; Evans, A.; Watt, H.; Lees, A.J. Low Dose Quetiapine for Drug Induced Dyskinesias in Parkinson’s Disease: A Double Blind Cross over Study. *J. Neurol. Neurosurg. Psychiatry* 2004, 75, 295–297.

122. Grunder, G.; Kungel, M.; Ebrecht, M.; Gorocs, T.; Modell, S. Aripiprazole: Pharmacodynamics of a Dopamine Partial Agonist for the Treatment of Schizophrenia. *Pharmacopsychiatry* 2006, 39 (Suppl. 1), S21–25. [CrossRef]

123. Friedman, J.H.; Berman, R.M.; Goetz, C.G.; Factor, S.A.; Ondo, W.G.; Wojcieszek, J.; Carson, W.H.; Marcus, R.N. Open-Label Flexible-Dose Pilot Study to Evaluate the Safety and Tolerability of Aripiprazole in Patients with Psychosis Associated with Parkinson’s Disease. *Mov. Disord.* 2006, 21, 2078–2081. [CrossRef] [PubMed]

124. Meco, G.; Stirpe, P.; Edito, F.; Purcaro, C.; Valente, M.; Bernardi, S.; Vanacore, N. Aripiprazole in Parkinsonian Marmoset. *Neuropharmacology* 2018, 139, 61–67. [CrossRef]

125. Anttila, S.A.K.; Leinonen, E.V.J. A Review of the Pharmacological and Clinical Profile of Mirtazapine. *CNS Drug Res* 2001, 7, 249–264. [CrossRef] [PubMed]

126. Hamadjida, A.; Nuara, S.G.; Gourdon, J.C.; Huot, P. The Effect of Mianserin on the Severity of Psychosis and Dyskinesia in the Parkinsonian Marmoset. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2018, 81, 367–371. [CrossRef] [PubMed]

127. Hamadjida, A.; Nuara, S.G.; Veyres, N.; Frouni, I.; Kwan, C.; Sid-Otmane, L.; Harraka, M.J.; Gourdon, J.C.; Huot, P. The Effect of Mirtazapine on Dopaminergic Psychosis and Dyskinesia in the Parkinsonian Marmoset. *Psychopharmacology* 2017, 234, 905–911. [CrossRef]
128. Meco, G.; Fabrizio, E.; Di Rezze, S.; Alessandri, A.; Pratesi, L. Mirtazapine in L-Dopa-Induced Dyskinesias. *Clin. Neuropharmacol.* 2003, 26, 179–181. [CrossRef]

129. Aboulghasemi, N.; Hadipour Jahromy, M.; Ghasemi, A. Anti-Dyskinetic Efficacy of 5-HT3 Receptor Antagonist in the Hemi-Parkinssonian Rat Model. *JBO Rep.* 2019, 6, 40–44. [CrossRef]

130. Asai, H.; Udaoka, F.; Hirano, M.; Minami, T.; Oda, M.; Kubori, T.; Nishinaka, K.; Kameyama, M.; Ueno, S. Increased Gastric Motility During 5-HT4 Agonist Therapy Reduces Response Fluctuations in Parkinson’s Disease. *Parkinsonism Relat. Disord.* 2005, 11, 499–502. [CrossRef]

131. Chase, T.N.; Oh, J.D.; Konitsiotis, S. Antiparkinsonian and Antidyskinetic Activity of Drugs Targeting Central Glutamatergic Mechanisms. *J. Neurol.* 2000, 247 (Suppl. 2), II36–42. [CrossRef]

132. Cenci, M.A. Glutamatergic Mechanisms in the Dyskinesias Induced by Pharmacological Dopamine Replacement and Deep Brain Stimulation for the Treatment of Parkinson’s Disease. *Prog. Neurobiol.* 2012, 96, 69–86. [CrossRef]

133. Liu, Y.; Liu, Z.; Li, F.; Kong, F. Therapeutic Effect of Mosapride Citrate on Gastrointestinal Tract Function Disorder of Patients with Parkinson’s Syndrome. *J. Jilin Univ. Med. Ed.* 2017, 43, 125–129.

134. Calon, F.; Rajput, A.H.; Hornykiewicz, O.; Bédard, P.J.; Di Paolo, T. Alteration of Glutamate Receptors in the Striatum of Dyskinetic 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Treated Monkeys Following Dopamine Agonist Treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2014, 39, 1366–1378. [CrossRef]

135. Cenci, M.A.; Ohlin, K.E.; Odin, P. Current Options and Future Possibilities for the Treatment of Dyskinesia and Motor Fluctuations in Parkinson’s Disease. *CNS Neurol. Disord. Drug Targets* 2011, 10, 670–684. [CrossRef]

136. Calon, F.; Morissette, M.; Ghribi, O.; Goulet, M.; Grondin, R.; Blanchet, P.J.; Bedard, P.J.; Di Paolo, T. Alteration of Glutamate Receptors in the Striatum of Dyskinetic 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Treated Monkeys Following Dopamine Agonist Treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2002, 26, 127–138. [CrossRef]

137. Calon, F.; Rajput, A.H.; Hornykiewicz, O.; Bédard, P.J.; Di Paolo, T. Levodopa-Induced Motor Complications Are Associated with Alterations of Glutamate Receptors in Parkinson’s Disease. *Neurobiol. Dis.* 2003, 14, 404–416. [CrossRef]

138. Chase, T.N.; Oh, J.D. Striatal Dopamine- and Glutamate-Mediated Dysregulation in Experimental Parkinsonism. *Trends Neurosci.* 2000, 23, S86–S91. [CrossRef]

139. Hadj Tahar, A.; Gregoire, L.; Darre, A.; Belanger, N.; Meltzer, L.; Bedard, P.J. Effect of a Selective Glutamate Antagonist on L-Dopa-Induced Dyskinesias in Drug-Naive Parkinsonian Monkeys. *Neurobiol. Dis.* 2004, 15, 171–176. [CrossRef]

140. Morissette, M.; Dridi, M.; Calon, F.; Tahar, A.H.; Meltzer, L.T.; Bédard, P.J.; Di Paolo, T. Prevention of Dyskinesia by an NMDA Receptor Antagonist in MPTP Monkeys: Effect on Adenosine A2A Receptors. *Synapse* 2006, 60, 239–250. [CrossRef]

141. Nash, J.E.; Fox, S.H.; Henry, B.; Hill, M.P.; Peggs, D.; McGuire, S.; Maneuf, Y.; Hille, C.; Brotchie, J.M.; Crossman, A.R. Antiparkinsonian Actions of fenprofion in the MPTP-Lesioned Marmoset Model of Parkinson’s Disease. *Exp. Neurol.* 2000, 165, 136–142. [CrossRef]

142. Nash, J.E.; Ravenscroft, P.; McGuire, S.; Crossman, A.R.; Mennti, F.S.; Brotchie, J.M. The NR2B-Selective NMDA Receptor Antagonist CP-101,606 Exacerbates L-DOPA-Induced Dyskinesia and Provides Mild Potentiation of Anti-Parkinsonian Effects of L-DOPA in the MPTP-Lesioned Marmoset Model of Parkinson’s Disease. *Exp. Neurol.* 2004, 188, 471–479. [CrossRef]
147. Nutt, J.G.; Gunzler, S.A.; Kirchhoff, T.; Hogarth, P.; Weaver, J.L.; Kram, M.; Jamerson, B.; Menniti, F.S.; Landen, J.W. Effects of a NR2B Selective NMDA Glutamate Antagonist, CP-101,606, on Dyskinesia and Parkinsonism. Mov. Disord. 2008, 23, 1860–1866. [CrossRef]

148. Igarashi, M.; Habata, T.; Akita, H.; Noda, K.; Ogata, M.; Saji, M. The NR2B Antagonist, Ifenprodil, Corrects the L-Dopa-Induced Deficit of Bilateral Movement and Reduces C-Fos Expression in the Subthalamic Nucleus of Hemiparkinsonian Rats. Neurosci. Res. 2015, 96, 45–53. [CrossRef]

149. Rylander, D.; Recchia, A.; Mela, F.; Dekundy, A.; Danysz, W.; Cenci, M.A. Pharmacological Modulation of Glutamate Transmission in a Rat Model of L-DOPA-Induced Dyskinesia: Effects on Motor Behavior and striatal Nuclear Signaling. J. Pharmacol. Exp. Ther. 2009, 330, 227–235. [CrossRef]

150. Wessell, R.H.; Ahmed, S.M.; Menniti, F.S.; Dunbar, G.L.; Chase, T.N.; Oh, J.D. NR2B Selective NMDA Receptor Antagonist CP-101,606 Prevents Levodopa-Induced Motor Response Alterations in Hemiparkinsonian Rats. Neuropharmacology 2004, 47, 184–194. [CrossRef]

151. Michel, A.; Downey, P.; Van Damme, X.; De Wolf, C.; Schwarting, R.; Scheller, D. Behavioural Assessment of the A2a/NR2B Combination in the Unilateral 6-OHDA-Lesioned Rat Model: A New Method to Examine the Therapeutic Potential of Non-Dopaminergic Drugs. PLoS ONE 2015, 10, e0135949. [CrossRef]

152. Wolf, E.; Seppi, K.; Katzenschlager, R.; Hochschorner, G.; Ransmayr, G.; Hochschorner, G.; Schwinger, J.; Otten, E.; Kloiber, I.; Haubenberger, D.; Auff, E.; et al. Long-Term Antidyskinetic Efficacy of Amantadine in Parkinson’s Disease. Mov. Disord. 2010, 25, 1357–1363. [CrossRef]

153. Sawada, H.; Oeda, T.; Kuno, S.; Nomoto, M.; Yamamoto, K.; Hisanaga, K.; Kawamura, T. Amantadine for Dyskinesias in Parkinson’s Disease: A Randomized Controlled Trial. PLoS ONE 2015, 10, e0182887. [CrossRef]

154. Snow, B.J.; Macdonald, L.; McAuley, D.; Wallis, W. The Effect of Amantadine on Levodopa-Induced Dyskinesias in Parkinson’s Disease: A Double-Blind, Placebo-Controlled Study. Clin. Neuropharmacol. 2000, 23, 82–85. [CrossRef] [PubMed]

155. Perez-Lloret, S.; Rascol, O. Efficacy and Safety of Amantadine for the Treatment of L-DOPA-Induced Dyskinesia. J. Neural Transm. 2018, 125, 1237–1250. [CrossRef] [PubMed]

156. Da Silva-Junior, F.P.; Braga-Neto, P.; Sueli Monte, F.; de Bruin, V.M. Amantadine Reduces the Duration of Levodopa-Induced Dyskinesia: A Randomized, Double-Blind, Placebo-Controlled Study. Parkinsonism Relat. Disord. 2005, 11, 449–452. [CrossRef] [PubMed]

157. Ory-Magne, F.; Corvol, J.C.; Azulay, J.P.; Bonnet, A.M.; Brefel-Courbon, C.; Damier, P.; Dellapina, E.; Destee, A.; Durif, F.; Galitzky, M.; et al. Withdrawing Amantadine in Dyskinetic Patients with Parkinson Disease: The Amandyak Trial. Neurology 2014, 82, 300–307. [CrossRef]

158. Thomas, A.; Iacono, D.; Luciano, A.L.; Armellino, A.; Onofrj, M. Duration of Amantadine Benefit on Dyskinesia of Severe Parkinson’s Disease. J. Neurol. Neurosurg. Psychiatry 2004, 75, 141–143. [PubMed]

159. Bortolanza, M.; Bariotto-Dos-Santos, K.D.; Dos-Santos-Pereira, M.; da-Silva, C.A.; Del-Bel, E. Antidyskinetic Effect of 7-Nitroindazole and Sodium Nitroprusside Associated with Amantadine in a Rat Model of Parkinson’s Disease. Neurotox. Res. 2016, 30, 88–100. [CrossRef]

160. Bortolanza, M.; Bariotto-Dos-Santos, K.D.; Dos-Santos-Pereira, M.; da-Silva, C.A.; Del-Bel, E. Antidyskinetic Effect of 7-Nitroindazole and Sodium Nitroprusside Associated with Amantadine in a Rat Model of Parkinson’s Disease. Neurotox. Res. 2016, 30, 88–100. [CrossRef]

161. Merello, M.; Noulle, M.I.; Cammarata, A.; Leiguarda, R. Effect of Memantine (NMDA Antagonist) on Parkinson’s Disease: A Double-Blind Crossover Randomized Study. Clin. Neuropharmacol. 1999, 22, 273–276.

162. Moreau, C.; Delval, A.; Tiffreau, V.; Defebvre, L.; Dujardin, K.; Duhamel, A.; Petyg, G.; Hossein-Fouchet, C.; Blum, D.; Sablonniere, B.; et al. Memantine for Axial Signs in Parkinson’s Disease: A Randomised, Double-Blind, Placebo-Controlled Pilot Study. J. Neurol. Neurosurg. Psychiatry 2013, 84, 552–555. [CrossRef]

163. Victorin, K.; Widner, H. Memantine and Reduced Time with Dyskinesia in Parkinson’s Disease. Acta Neurol. Scand. 2016, 133, 355–360. [CrossRef] [PubMed]

164. Paquette, M.A.; Anderson, A.M.; Lewis, J.R.; Meshul, C.K.; Johnson, S.W.; Paul Berger, S. MK-801 Inhibits L-DOPA-Induced Abnormal Involuntary Movements Only at Doses That Worsen Parkinsonism. Neuropharmacology 2010, 58, 1002–1008. [CrossRef] [PubMed]
165. Flores, A.J.; Bartlett, M.J.; Root, B.K.; Parent, K.L.; Heien, M.L.; Porreca, F.; Polt, R.; Sherman, S.J.; Falk, T. The Combination of the Opioid Glycopeptide MMP-2200 and a NMDA Receptor Antagonist Reduced L-Dopa-Induced Dyskinesia and MMP-2200 by Itself Reduced Dopamine Receptor 2-Like Agonist-Induced Dyskinesia. *Neuropharmacology* 2018, 141, 260–271. [CrossRef] [PubMed]

166. Bartlett, M.J.; Joseph, R.M.; LePoidevin, L.M.; Parent, K.L.; Laude, N.D.; Lazarus, L.B.; Heien, M.L.; Estevez, M.; Sherman, S.J.; Falk, T. Long-Term Effect of Sub-Anesthetic Ketamine in Reducing L-DOPA-Induced Dyskinesias in a Preclinical Model. *Neurosci. Lett.* 2016, 612, 121–125. [CrossRef] [PubMed]

167. Sherman, S.J.; Estevez, M.; Magill, A.B.; Falk, T. Case Reports Showing a Long-Term Effect of Subanesthetic Ketamine Infusion in Reducing L-Dopa-Induced Dyskinesias. *Case Rep. Neurol.* 2016, 8, 53–58. [CrossRef] [PubMed]

168. Santini, E.; Sgambato-Faure, V.; Li, Q.; Savasta, M.; Dovero, S.; Fisone, G.; Bezard, E. Distinct Changes in cAMP and Extracellular Signal-Regulated Protein Kinase Signalling in L-DOPA-Induced Dyskinesia. *PLoS ONE* 2010, 5, e12322. [CrossRef] [PubMed]

169. Santini, E.; Valjent, E.; Usiello, A.; Carta, M.; Borgkvist, A.; Girault, J.A.; Herve, D.; Greengard, P.; Fisone, G. Critical Involvement of cAMP-DARPP-32 and Extracellular Signal-Regulated Protein Kinase Signaling in L-DOPA-Induced Dyskinesia. *J. Neurosci.* 2007, 27, 6995–7005. [CrossRef]

170. Ba, M.; Kong, M.; Yang, H.; Ma, G.; Lu, G.; Chen, S.; Liu, Z. Changes in Subcellular Distribution and Phosphorylation of GluR1 in Lesioned Striatum of 6-Hydroxydopamine-Lesioned and L-Dopa-Treated Rats. *Neurochem. Res.* 2006, 31, 1337–1347. [CrossRef]

171. Errico, F.; Bonito-Oliva, A.; Bagetta, V.; Vitucci, D.; Romano, R.; Zianni, E.; Napolitano, F.; Marinucci, S.; Di Luca, M.; Calabresi, P.; et al. Higher Free D-Aspartate and N-Methyl-D-Aspartate Levels Prevent Striatal Depotentiation and Anticipate L-DOPA-Induced Dyskinesia. *Exp. Neurol.* 2011, 232, 240–250. [CrossRef]

172. Bibbiano, F.; Oh, J.D.; Kielaita, A.; Collins, M.A.; Smith, C.; Chase, T.N. Combined Blockade of AMPA and NMDA Glutamate Receptors Reduces Levodopa-Induced Motor Complications in Animal Models of PD. *Exp. Neurol.* 2005, 196, 422–429. [CrossRef]

173. Kobylecki, C.; Cenci, M.A.; Crossman, A.R.; Ravenscroft, P. Calcium-Permeable AMPA Receptors Are Involved in the Induction and Expression of L-Dopa-Induced Dyskinesia in Parkinson’s Disease. *J. Neurochem.* 2010, 114, 499–511. [CrossRef]

174. Konitsiotis, S.; Blanchet, P.J.; Verhagen, L.; Lamers, E.; Chase, T.N. AMPA Receptor Blockade Improves Levodopa-Induced Dyskinesia in MPTP Monkeys. *Neurology* 2000, 54, 1589–1595. [CrossRef]

175. Vijayakumar, D.; Jankovic, J. Drug-Induced Dyskinesia, Part 1: Treatment of Levodopa-Induced Dyskinesia. *Drugs* 2016, 76, 759–777. [CrossRef]

176. White, H.S.; Brown, S.D.; Woodhead, J.H.; Skeen, G.A.; Wolf, H.H. Topiramate Modulates GABA-Evoked Currents in Murine Cortical Neurons by a Nonbenzodiazepine Mechanism. *Epilepsia* 2000, 41 (Suppl. 1), S17–20. [CrossRef]

177. Silverdale, M.A.; Nicholson, S.L.; Crossman, A.R.; Brotchie, J.M. Topiramate Reduces Levodopa-Induced Dyskinesia in the MPTP-Lesioned Marmoset Model of Parkinson’s Disease. *Mov. Disord.* 2005, 20, 403–409. [CrossRef]

178. Kobylecki, C.; Hill, M.P.; Crossman, A.R.; Ravenscroft, P. Synergistic Antidysskinetic Effects of Topiramate and Amantadine in Animal Models of Parkinson’s Disease. *Mov. Disord.* 2011, 26, 2354–2363. [CrossRef]

179. Kobylecki, C.; Burn, D.J.; Kass-Iliyva, L.; Kellett, M.W.; Crossman, A.R.; Silverdale, M.A. Randomized Clinical Trial of Topiramate for Levodopa-Induced Dyskinesia in Parkinson’s Disease. *Parkinsonism Relat. Disord.* 2014, 20, 452–455. [CrossRef]

180. Eggert, K.; Squillacote, D.; Barone, P.; Dedol, R.; Katzenschlager, R.; Emre, M.; Lees, A.J.; Rascol, O.; Poewe, W.; Tolosa, E.; et al. Safety and Efficacy of Perampanel in Advanced Parkinson’s Disease: A Randomized, Placebo-Controlled Study. *Mov. Disord.* 2010, 25, 896–905. [CrossRef]

181. Lees, A.; Fahn, S.; Eggert, K.M.; Jankovic, J.; Lang, A.; Micheli, F.; Maral Mouradian, M.; Oertel, W.H.; Olanow, C.W.; Poewe, W.; et al. Perampanel, an AMPA Antagonist, Found to Have No Benefit in Reducing “Off” Time in Parkinson’s Disease. *Mov. Disord.* 2012, 27, 284–288. [CrossRef]

182. Rascol, O.; Barone, P.; Behari, M.; Emre, M.; Giladi, N.; Olanow, C.W.; Ruzicka, E.; Bibbiano, F.; Squillacote, D.; Patten, A.; et al. Perampanel in Parkinson Disease Fluctuations: A Double-Blind Randomized Trial with Placebo and Entacapone. *Clin. Neuropharmacol.* 2012, 35, 15–20. [CrossRef]
183. Marin, C.; Jimenez, A.; Bonastre, M.; Vila, M.; Agid, Y.; Hirsch, E.C.; Tolosa, E. Ly293558, an AMPA Glutamate Receptor Antagonist, Prevents and Reverses Levodopa-Induced Motor Alterations in Parkinsonian Rats. *Synapse* 2001, 42, 40–47. [CrossRef]

184. Litin, N.; Morissette, M.; Di Paolo, T. Metabotropic Glutamate Receptors as Therapeutic Targets in Parkinson’s Disease: An Update from the Last 5 Years of Research. *Neuropsychopharmacology* 2017, 115, 166–179. [CrossRef]

185. Sebastianutto, I.; Cenci, M.A. mGlu Receptors in the Treatment of Parkinson’s Disease and L-DOPA-Induced Dyskinesia. *Curr. Opin. Pharm.* 2018, 38, 81–89. [CrossRef]

186. Murray, T.K.; Messenger, M.J.; Ward, M.A.; Woodhouse, S.; Osborne, D.J.; Duty, S.; O’Neill, M.J. Evaluation of the mGluR2/3 Agonist LY379268 in Rodent Models of Parkinson’s Disease. *Pharmacol. Biochem. Behav.* 2002, 73, 455–466. [CrossRef]

187. Amalric, M.; Lopez, S.; Goudet, C.; Fisone, G.; Battaglia, G.; Nicoletti, F.; Pin, J.P.; Acher, F.C. Group III and Subtype 4 Metabotropic Glutamate Receptor Agonists: Discovery and Pathophysiological Applications in Parkinson’s Disease. *Neuropsychopharmacology* 2013, 36, 53–64. [CrossRef]

188. Le Poul, E.; Bolea, C.; Girard, F.; Poli, S.; Charvin, D.; Campo, B.; Bortoli, J.; Bessis, A.; Luo, B.; Koser, A.J.; et al. A Potent and Selective Metabotropic Glutamate Receptor 4 Positive Allosteric Modulator Improves Movement in Rodent Models of Parkinson’s Disease. *J. Pharmocol. Exp. Ther.* 2012, 343, 167–177. [CrossRef]

189. Bennouar, K.E.; Uberti, M.A.; Melon, C.; Bacolod, M.D.; Jimenez, H.N.; Cajina, M.; Kerkerian-Le Go, C.; et al. Discovery, Structure-Activity Relationship, and Antiparkinsonian Effect of a Potent and Brain-Penetrant Chemical Series of Positive Allosteric Modulators of Metabotropic Glutamate Receptor 4. *J. Med. Chem.* 2017, 60, 8515–8537. [CrossRef]

190. Charvin, D.; Di Paolo, T.; Bezdard, E.; Greco, L.; Takano, A.; Duvey, G.; Pioli, E.; Halldin, C.; Medori, R.; Conquet, F. An Mglu4-Positive Allosteric Modulator Alleviates Parkinsonism in Primates. *Mov. Disord.* 2018, 33, 1619–1631. [CrossRef] [PubMed]

191. Marin, C.; Bonastre, M.; Aguilar, E.; Jimenez, A. The Metabotropic Glutamate Receptor Antagonist 2-Methyl-6-(Phenylethynyl) Pyridine Decreases Striatal VGlut2 Expression in Association with an Attenuation of L-DOPA-Induced Dyskinesias. *Synapse* 2011, 65, 1080–1086. [CrossRef] [PubMed]

192. Mela, F.; Marti, M.; Dekundy, A.; Danysz, W.; Morari, M.; Cenci, M.A. Antagonism of Metabotropic Glutamate Receptor Type 5 Attenuates L-Dopa-Induced Dyskinesia and Its Molecular and Neurochemical Correlates in a Rat Model of Parkinson’s Disease. *J. Neurochem.* 2007, 101, 483–497. [CrossRef]

193. Morin, N.; Greco, L.; Gomez-Mancilla, B.; Gasparini, F.; Di Paolo, T. Effect of the Metabotropic Glutamate Receptor Type 5 Antagonists MPEP and MTEP in Parkinsonian Monkeys. *Neuropsychopharmacology* 2010, 35, 981–986. [CrossRef] [PubMed]

194. Morin, N.; Morissette, M.; Greco, L.; Gomez-Mancilla, B.; Gasparini, F.; Di Paolo, T. Chronic Treatment with MPEP, an mGlu5 Receptor Antagonist, Normalizes Basal Ganglia Glutamate Neurotransmission in L-DOPA-Treated Parkinsonian Monkeys. *Neuropsychopharmacology* 2013, 73, 216–231. [CrossRef] [PubMed]

195. Rylander, D.; Iderberg, H.; Li, Q.; Dekundy, A.; Zhang, J.; Li, H.; Baishen, R.; Danysz, W.; Bezdard, E.; Cenci, M.A. A mGluR5 Antagonist under Clinical Development Improves L-DOPA-Induced Dyskinesia in Parkinsonian Rats and Monkeys. *Neurobiol. Dis.* 2010, 39, 352–361. [CrossRef]

196. Ko, W.K.; Pioli, E.; Li, Q.; McGuire, S.; Dufour, A.; Sherer, T.B.; Bezdard, E.; Facheris, M.F. Combined Fenebamb and Amantadine Treatment Promotes Robust Antidyshkinetic Effects in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-Lesioned Primate Model of Parkinson’s Disease. *Mov. Disord.* 2014, 29, 772–779. [CrossRef]
200. Mavridis, M.; Degryse, A.D.; Lategan, A.J.; Marien, M.R.; Colpaert, F.C.; et al. Dual Target Strategy: Combining Distinct Non-Dopaminergic Treatments Reduces Neuronal Cell Loss and Synergistically Modulates L-DOPA-Induced Rotational Behavior in a Rodent Model of Parkinson’s Disease. *J. Neurochem.* 2015, 134, 740–747. [CrossRef]

201. Berg, D.; Godau, J.; Trenkwalder, C.; Eggert, K.; Cstoi, I.; Storch, A.; Huber, H.; Morelli-Canelo, M.; Stamelou, M.; Ries, V.; et al. AFQ056 Treatment of Levodopa-Induced Dyskinesias: Results of 2 Randomized Controlled Trials. *Mov. Disord.* 2011, 26, 1243–1250. [CrossRef]

202. Fuzzati-Armentero, M.T.; Cerri, S.; Levandis, G.; Ambrosi, G.; Montepeloso, E.; Antoninetti, G.; Blandini, F.; Baqi, Y.; Muller, C.E.; Volpini, R.; et al. Contribution of the mGluR7 Receptor to Antiparkinsonian-Like Effects of 1,2,3,6-Tetrahydropyridine in Monkeys: A Possible Role for the Locus Coeruleus in the Progression of Parkinson’s Disease and Alzheimer’s Disease. *Biomolecules* 2016, 31, 1054–1058. [CrossRef]

203. Konieczny, J.; Lenda, T. Contribution of the mGluR7 Receptor to Antiparkinsonian-Like Effects in Rats: A Behavioral Study with the Selective Agonist AMN082. *Pharmacol. Rep.* 2013, 65, 1194–1203. [CrossRef]

204. Johnson, K.A.; Jones, C.K.; Tantawy, M.N.; Bubser, M.; Marvanova, M.; Ansari, M.S.; Baldwin, R.M.; Conn, P.J.; Niswender, C.M. The Metabotropic Glutamate Receptor 8 Agonist (S)-3,4-DCPG Reverses Motor Deficits in Prolonged but Not Acute Models of Parkinson’s Disease. *Neuropharmacology* 2013, 66, 187–195. [CrossRef] [PubMed]

205. Kuhn, R.; McAllister, K.H.; et al. A Selective Metabotropic Glutamate Receptor 7 Agonist: Activation of Receptor Signaling Via an Allosteric Site Modulates Stress Parameters in Vivo. *Proc. Natl. Acad. Sci. USA* 2005, 102, 18712–18717. [CrossRef] [PubMed]

206. Konieczny, J.; Lenda, T. Contribution of the mGluR7 Receptor to Antiparkinsonian-Like Effects in Rats: A Behavioral Study with the Selective Agonist AMN082. *Pharmacol. Rep.* 2013, 65, 1194–1203. [CrossRef]

207. Fornai, F.; di Poggio, A.B.; Pellegrini, A.; Ruggieri, S.; Paparelli, A. Noradrenaline in Parkinson’s Disease: From Differential Effects in Rats: A Possible Role for the Locus Coeruleus in the Progression of Parkinson’s Disease. *Brain Res.* 2011, 1373, 240–252. [CrossRef]

208. Johnson, K.A.; Jones, C.K.; Tantawy, M.N.; Bubser, M.; Marvanova, M.; Ansari, M.S.; Baldwin, R.M.; Conn, P.J.; Niswender, C.M. The Metabotropic Glutamate Receptor 8 Agonist (S)-3,4-DCPG Reverses Motor Deficits in Prolonged but Not Acute Models of Parkinson’s Disease. *Neuropharmacology* 2013, 66, 187–195. [CrossRef] [PubMed]

209. Foote, S.L.; Bloom, F.E.; Aston-Jones, G. Nucleus Locus Ceruleus: New Evidence of Anatomical and Physiological Specificity. *Physiol. Rev.* 1983, 63, 844–914. [CrossRef] [PubMed]

210. Zarow, C.; Lymess, S.A.; Mortimer, J.A.; Chui, H.C. Neuronal Loss Is Greater in the Locus Coeruleus Than Nucleus Basalis and Substantia Nigra in Alzheimer and Parkinson Diseases. *Arch. Neurol.* 2003, 60, 337–341. [CrossRef] [PubMed]

211. Berg, D.; Godau, J.; Trenkwalder, C.; Eggert, K.; Cstoi, I.; Storch, A.; Huber, H.; Morelli-Canelo, M.; Stamelou, M.; Ries, V.; et al. AFQ056 Treatment of Levodopa-Induced Dyskinesias: Results of 2 Randomized Controlled Trials. *Mov. Disord.* 2011, 26, 1243–1250. [CrossRef]

212. Trenkwalder, C.; Stocchi, F.; Poewe, W.; Dronamraju, N.; Kenney, C.; Shah, A.; von Raison, F.; Graf, A. Mavoglurant in Parkinson’s Patients with L-Dopa-Induced Dyskinesias: Two Randomized Phase 2 Studies. *Mov. Disord.* 2016, 31, 1054–1058. [CrossRef]

213. McMillan, P.J.; White, S.S.; Franklin, A.; Greenup, J.L.; Leverenz, J.B.; Raskind, M.A.; Szot, P.D.; et al. Noradrenaline in Parkinson’s Disease: From Differential Effects in Rats: A Possible Role for the Locus Coeruleus in the Progression of Parkinson’s Disease. *Brain Res.* 2011, 1373, 240–252. [CrossRef]
217. Barnum, C.J.; Bhide, N.; Lindenbach, D.; Surrena, M.A.; Goldenberg, A.A.; Tignor, S.; Klioueva, A.; Walters, H.; Bishop, C. Effects of Noradrenergic Denervation on L-DOPA-Induced Dyskinesia and Its Treatment by A- and B-Adrenergic Receptor Antagonists in Hemiparkinsonian Rats. Pharmacol. Biochem. Behav. 2012, 100, 607–615. [CrossRef]
218. Rascol, O.; Arnulf, I.; Peyro-Saint Paul, H.; Brefel-Courbon, C.; Vidailhet, M.; Thalamas, C.; Bonnet, A.M.; Descombes, S.; Bejiani, B.; Fabre, N.; et al. Idazoxan, an Alpha-2 Antagonist, and L-DOPA-Induced Dyskinesias in Patients with Parkinson’s Disease. Mov. Disord. 2001, 16, 708–713. [CrossRef]
219. Johnston, T.H.; Fox, S.H.; Piggott, M.J.; Savola, J.M.; Brotchie, J.M. The Alpha(2) Adrenergic Antagonist Fipamezole Improves Quality of Levodopa Action in Parkinsonian Primates. Mov. Disord. 2010, 25, 2084–2093. [CrossRef]
220. Dimitrova, T.; Bara-Jimenez, W.; Savola, J.; Encarnacion, E.; Mouradian, M.; Chase, T. Alpha-2 Adrenergic Antagonist Effects in Parkinson’s Disease; Neurology, 2011; Lippincott Williams & Wilkins 530 Walnut St: Philadelphia, PA, USA; p. A540.
221. Lewitt, P.A.; Hauser, R.A.; Lu, M.; Nicholas, A.P.; Weiner, W.; Coppard, N.; Leinonen, M.; Savola, J.M. Randomized Clinical Trial of Fipamezole for Dyskinesia in Parkinson Disease (Fjord Study). Neurology 2012, 79, 163–169. [CrossRef]
222. Rainbow, T.C.; Parsons, B.; Wolfe, B.B. Quantitative Autoradiography of Beta 1- and Beta 2-Adrenergic Receptors in Rat Brain. Proc. Natl. Acad. Sci. USA 1984, 81, 1585–1589. [CrossRef]
223. Waeber, C.; Rigo, M.; Chinaglia, G.; Probst, A.; Palacios, J.M. Beta-Adrenergic Receptor Subtypes in the Basal Ganglia of Patients with Huntington’s Chorea and Parkinson’s Disease. Synapse 1991, 8, 270–280. [CrossRef]
224. Bhide, N.; Lindenbach, D.; Barnum, C.J.; George, J.A.; Surrerna, M.A.; Bishop, C. Effects of the Beta-Adrenergic Receptor Antagonist Propranolol on Dyskinesia and L-DOPA-Induced Striatal Da Efflux in the Hemi-Parkinsonian Rat. J. Neurochem. 2015, 134, 222–232. [CrossRef]
225. Pagano, G.; Tan, E.E.; Haider, J.M.; Bautista, A.; Tagliati, M. Constipation Is Reduced by Beta-Blockers and Increased by Dopaminergic Medications in Parkinson’s Disease. Parkinsonism Relat. Disord. 2015, 21, 120–125. [CrossRef]
226. Julius, A.; Longfellow, K. Movement Disorders: A Brief Guide in Medication Management. Med. Clin. N. Am. 2016, 100, 733–761. [CrossRef]
227. Magistrelli, L.; Comi, C. Beta2-Adrenoceptor Agonists in Parkinson’s Disease and Other Synucleinopathies. J. Neuroimmune Pharmacol. 2019. [CrossRef]
228. Latini, S.; Pedata, F. Adenosine in the Central Nervous System: Release Mechanisms and Extracellular Concentrations. J. Neurochem. 2001, 79, 463–484. [CrossRef]
229. Ferré, S. Adenosine-Dopamine Interactions in the Ventral Striatum. Implications for the Treatment of Schizophrenia. Psychopharmacology 1997, 133, 107–120.
230. Ferré, S.; Popoli, P.; Giménez-Lloré, L.; Rimondini, R.; Müller, C.E.; Strömberg, I.; Ögren, S.O.; Fuxe, K. Adenosine/Dopamine Interaction: Implications for the Treatment of Parkinson’s Disease. Parkinsonism Relat. Disord. 2001, 7, 235–241. [CrossRef]
231. Fastbom, J.; Pazos, A.; Palacios, J.M. The Distribution of Adenosine A1 Receptors and 5’-Nucleotidase in the Brain of Some Commonly Used Experimental Animals. Neuroscience 1987, 22, 813–826. [CrossRef]
232. Mango, D.; Bonito-Oliva, A.; Ledonne, A.; Cappellacci, L.; Petrelli, R.; Nistico, R.; Berretta, N.; Fisone, G.; Mercuri, N.B. Adenosine A1 Receptor Stimulation Reduces D1 Receptor-Mediated Gabaergic Transmission from Striato-Nigral Terminals and Attenuates L-Dopa-Induced Dyskinesia in Dopamine-Denervated Mice. Exp. Neurol. 2014, 261, 733–743. [CrossRef]
233. Fastbom, J.; Pazos, A.; Palacios, J.M. The Distribution of Adenosine A1 Receptors and 5’-Nucleotidase in the Brain of Some Commonly Used Experimental Animals. Neuroscience 1987, 22, 813–826. [CrossRef]
234. Pollack, A.E.; Fink, J.S. Adenosine Antagonists Potentiate D2 Dopamine-Dependent Activation of Fos in the Striatopallidal Pathway. Neuroscience 1995, 68, 721–728. [CrossRef]
235. Zheng, J.; Zhang, X.; Zhen, X. Development of Adenosine A2A Receptor Antagonists for the Treatment of Parkinson’s Disease: A Recent Update and Challenge. ACS Chem. Neurosci. 2019, 10, 783–791. [CrossRef]
236. Approval for Manufacturing and Marketing of Nouriast Tablets 20 Mg, a Novel Antiparkinsonian Agent, Kyowa Hakko Kirin Co Ltd Press Release. 25 March 2019. Available online: https://www.kyowa-kirin.com/news_releases/2013/c20130325_04.html (accessed on 9 April 2019).
237. Lundblad, M.; Vaudano, E.; Cenci, M.A. Cellular and Behavioural Effects of the Adenosine A2a Receptor Antagonist KW-6002 in a Rat Model of L-Dopa-Induced Dyskinesia. J. Neurochem. 2003, 84, 1398–1410. [CrossRef]

238. Kanda, T.; Jackson, M.J.; Smith, L.A.; Pearce, R.K.; Nakamura, J.; Kase, H.; Kuwana, Y.; Jenner, P. Adenosine A2A Antagonist: A Novel Antiparkinsonian Agent That Does Not Provoke Dyskinesia in Parkinsonian Monkeys. Ann. Neurol. 1998, 43, 507–513. [CrossRef] [PubMed]

239. Kanda, T.; Tashiro, T.; Kuwana, Y.; Jenner, P. Adenosine A2A Receptors Modify Motor Function in MPTP-Treated Common Marmosets. Neuroreport 1998, 9, 2857–2860. [CrossRef]

240. Kanda, T.; Jackson, M.J.; Smith, L.A.; Pearce, R.K.; Nakamura, J.; Kase, H.; Kuwana, Y.; Jenner, P. Combined Use of the Adenosine A(2A) Antagonist KW-6002 with L-DOPA or with Selective D1 or D2 Dopamine Agonists Increases Antiparkinsonian Activity but Not Dyskinesia in MPTP-Treated Monkeys. Exp. Neurol. 2000, 162, 321–327. [CrossRef]

241. Uchida, S.; Tashiro, T.; Kawai-Uchida, M.; Mori, A.; Jenner, P.; Kanda, T. Adenosine a(2)a-Receptor Antagonist Istradefylline Enhances the Motor Response of L-DOPA without Worsening Dyskinesia in MPTP-Treated Common Marmosets. J. Pharmacol. Sci. 2014, 124, 480–485. [CrossRef]

242. Bibbiani, F.; Oh, J.D.; Petzer, J.P.; Castagnoli, N., Jr.; Chen, J.F.; Schwarzschild, M.A.; Chase, T.N. A2A Antagonist Prevents Dopamine Agonist-Induced Motor Complications in Animal Models of Parkinson’s Disease. Neurology 2003, 52, 1673–1677. [CrossRef]

243. Ko, W.K.D.; Camus, S.M.; Li, Q.; Yang, J.; McGuire, S.; Pioli, E.Y.; Bezard, E. An Evaluation of Istradefylline Treatment on Parkinsonian Motor and Cognitive Deficits in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-Treated Macaque Models. Neuropharmacology 2016, 110, 48–58. [CrossRef]

244. Hauser, R.A.; Shulman, L.M.; Trugman, J.M.; Roberts, J.W.; Mori, A.; Ballerini, R.; Sussman, N.M. Study of Istradefylline in Patients with Parkinson’s Disease on Levodopa with Motor Fluctuations. Mov. Disord. 2008, 23, 2177–2185. [CrossRef]

245. Hauser, R.A.; Hubble, J.P.; Hadj Tahar, A.; Gregoire, L.; Mori, A.; Kase, H. Antiparkinsonian Effect of a New Selective Adenosine A2A Receptor Antagonist in MPTP-Treated Monkeys. Neurology 1999, 52, 1673–1677. [CrossRef]

246. LeWitt, P.A.; Guttman, M.; Tetrud, J.W.; Tuite, P.J.; Mori, A.; Chaikin, P.; Sussman, N.M.; Group, U.S.S. Adenosine A2A Receptor Antagonist Istradefylline (KW-6002) Reduces “Off” Time in Parkinson’s Disease: A Double-Blind, Randomized, Multicenter Clinical Trial (6002-US-005). Ann. Neurol. 2008, 63, 297–302. [CrossRef]

247. Zhu, C.; Wang, G.; Li, J.; Chen, L.; Wang, C.; Wang, Y.; Lin, P.; Ran, H. Adenosine A2A Receptor Antagonist Istradefylline 20 Versus 40 Mg/Day as Augmentation for Parkinson’s Disease: A Meta-Analysis. Mov. Disord. 2014, 36, 1028–1034. [CrossRef]

248. Takahashi, M.; Fujita, M.; Asai, N.; Saki, M.; Mori, A.; Safety and Efficacy of Istradefylline in Patients with Parkinson’s Disease: Interim Analysis of a Post-Marketing Surveillance Study in Japan. Expert Opin. Pharmacother. 2018, 19, 1635–1642. [CrossRef]

249. Torti, M.; Vacca, L.; Stocchi, F. Istradefylline for the Treatment of Parkinson’s Disease: Is It a Promising Strategy? Expert Opin. Pharmacother. 2018, 19, 1821–1828. [CrossRef]
255. Hodgson, R.A.; Bertorelli, R.; Varty, G.B.; Lachowicz, J.E.; Forlani, A.; Freduzzi, S.; Cohen-Williams, M.E.; Higgins, G.A.; Impagnatiello, F.; Nicollusi, E.; et al. Characterization of the Potent and Highly Selective A2A Receptor Antagonists Preladenant and SCH 412348 [7-[2-[4-(2,4-Difluorophenyl)-1-piperazinyl]ethyl]-2-(2-furanyl)-7h-Pyrazolo [4,3-E][1,2,4]Triazolo [1,5-C]Pyrimidin-5-amine] in Rodent Models of Movement Disorders and Depression. J. Pharmacol. Exp. Ther. 2009, 330, 294–303.

256. Factor, S.A.; Wolski, K.; Togasaki, D.M.; Huyck, S.; Cantillon, M.; Ho, T.W.; Hauser, R.A.; Pourcher, E. Long-Term Safety and Efficacy of Preladenant in Subjects with Fluctuating Parkinson’s Disease. Mov. Disord. 2013, 28, 817–820. [CrossRef]

257. Hauser, R.A.; Cantillon, M.; Pourcher, E.; Michel, F.; Mok, V.; Onofrj, M.; Huyck, S.; Wolski, K. Preladenant in Patients with Parkinson’s Disease and Motor Fluctuations: A Phase 2, Double-Blind, Randomised Trial. Lact. Neurol. 2011, 10, 221–229. [CrossRef]

258. Hattori, N.; Kikuchi, M.; Adachi, N.; Hewitt, D.; Huyck, S.; Saito, T. Adjunctive Preladenant: A Placebo-Controlled, Dose-Finding Study in Japanese Patients with Parkinson’s Disease. Parkinsonism Relat. Disord. 2016, 32, 73–79. [CrossRef]

259. Hauser, R.; Stocchi, F.; Rascol, O.; Huyck, S.; Ha, X.; Capece, R.; Wolski, K.; Ho, T.; Sklar, P.; Lines, C.; et al. Phase-3 Clinical Trials of Adjunctive Therapy with Preladenant, an Adenosine 2a Antagonist, in Patients with Parkinson’s Disease (P7.087). Neurology 2014, 82, P7.087.

260. Hauser, R.A.; Stocchi, F.; Rascol, O.; Huyck, S.B.; Capece, R.; Ho, T.W.; Sklar, P.; Lines, C.; Michelon, D.; Hewitt, D. Preladenant as an Adjunctive Therapy with Levodopa in Parkinson Disease: Two Randomized Clinical Trials and Lessons Learned. JAMA neural 2015, 72, 1491–1500. [CrossRef]

261. Black, K.J.; Kolier, J.M.; Campbell, M.C.; Gusnard, D.A.; Bandak, S.I. Quantification of Indirect Pathway Inhibition by the Adenosine A2a Antagonist SYN115 in Parkinson Disease. J. Neurosci. 2010, 30, 16284–16292. [CrossRef]

262. Hauser, R.A.; Olanow, C.W.; Kieburz, K.D.; Pourcher, E.; Docu-Axlerad, A.; Lew, M.; Kozyolkin, O.; Neale, A.; Resburg, C.; Mey, U.; et al. Tozadenant (SYN115) in Patients with Parkinson’s Disease Who Have Motor Fluctuations on Levodopa: A Phase 2b, Double-Blind, Randomised Trial. Lactet. Neurol. 2014, 13, 767–776. [CrossRef]

263. Papapetropoulos, S.; Borgohain, R.; Kellet, M.; Giladi, N.; Tomic, D.; Coppell, A. The Adenosine A2A Receptor Antagonist BIIB014 Is Effective in Improving on-Time in Parkinson’s Disease (PD) Patients with Motor Fluctuations. Mov. Disord. 2010, 25, S305.

264. Pawsey, S.; Donaldson, K.; Warrington, S.; Tranter, E. A Phase I Single and Repeated Dose Pharmacokinetic Study of Oral V81444, a Selective Non-Xanthine Adenosine A2A Receptor Antagonist. J. Neurol. Sci. 2013, 333, e135. [CrossRef]

265. Núñez, F.; Taura, J.; Camacho, J.; López-Can, M.; Fernández-Dueñas, V.; Castro, N.; Castro, J.; Ciruela, F.; PBF509, an Adenosine A(2A) Receptor Antagonist with Efficacy in Rodent Models of Movement Disorders. Front. Pharmacol. 2018, 9, 1200. [CrossRef]

266. Tronci, E.; Simola, N.; Borsini, F.; Schintu, N.; Frau, L.; Carminati, P.; Morelli, M. Characterization of the Antiparkinsonian Effects of the New Adenosine A2A Receptor Antagonist ST1535: Acute and Subchronic Studies in Rats. Eur. J. Pharmacol. 2007, 566, 94–102. [CrossRef]

267. Rose, S.; Ramsay Croft, N.; Jenner, P. The Novel Adenosine A2a Antagonist ST1535 Potentiates the Effects of a Threshold Dose of L-Dopa in Unilaterally 6-OHDA-Lesioned Rats. Brain Res. 2007, 1133, 110–114. [CrossRef]

268. Rose, S.; Jackson, M.J.; Smith, L.A.; Stockwell, K.; Johnson, L.; Carminati, P.; Jenner, P. The Novel Adenosine A2a Receptor Antagonist ST1535 Potentiates the Effects of a Threshold Dose of L-DOPA in MPTP Treated Common Marmosets. Eur. J. Pharmacol. 2006, 546, 82–87. [CrossRef]

269. Pinna, A. Adenosine A2A Receptor Antagonists in Parkinson’s Disease: Progress in Clinical Trials from the Newly Approved Istradefylline to Drugs in Early Development and Those Already Discontinued. CNS Drugs 2014, 28, 455–474. [CrossRef]

270. Bagga, P.; Chugani, A.,N.; Patel, A.B. Neuroprotective Effects of Caffeine in MPTP Model of Parkinson’s Disease: A (13)C NMR Study. Neurochem. Int. 2016, 92, 25–34. [CrossRef]

271. Rivera-Oliver, M.; Díaz-Rios, M. Using Caffeine and Other Adenosine Receptor Antagonists and Agonists as Therapeutic Tools against Neurodegenerative Diseases: A Review. Life Sci. 2014, 101, 1–9. [CrossRef]
272. Roshan, M.H.; Tambo, A.; Pace, N.P. Potential Role of Caffeine in the Treatment of Parkinson’s Disease. Open Neurol. J. 2016, 10, 42–58. [CrossRef]

273. Wills, A.-M.A.; Eberly, S.; Tennis, M.; Lang, A.E.; Messing, S.; Togasaki, D.; Tanner, C.M.; Kamp, C.; Chen, J.-F.; Oakes, D.; et al. Caffeine Consumption and Risk of Dyskinesia in Calm-PD. Mov. Disord. 2013, 28, 380–383. [CrossRef]

274. Postuma, R.B.; Lang, A.E.; Munhoz, R.P.; Charland, K.; Pelletier, A.; Moscovitch, M.; Filla, L.; Zanatta, D.; Rios Romenets, S.; Altman, R.; et al. Caffeine for Treatment of Parkinson Disease: A Randomized Controlled Trial. Neurology 2012, 79, 651–658. [CrossRef]

275. Pilleri, M.; Antonini, A. Therapeutic Strategies to Prevent and Manage Dyskinesias in Parkinson’s Disease. Expert Opin. Drug Saf. 2015, 14, 281–294. [CrossRef]

276. Lim, S.A.O.; Xia, R.; Ding, Y.; Won, L.; Ray, W.J.; Hitchcock, S.A.; McGehee, D.S.; Kang, U.J. Enhanced Histamine H2 Excitation of Striatal Cholinergic Interneurons in L-DOPA-Induced Dyskinesia. Neurobiol. Dis. 2015, 76, 67–76. [CrossRef] [PubMed]

277. Johnston, T.H.; van der Melj, A.; Brochier, J.M.; Fox, S.H. Effect of Histamine H2 Receptor Antagonism on Levodopa-Induced Dyskinesia in the MPTP-Macaque Model of Parkinson’s Disease. Mov. Disord. 2010, 25, 1379–1390. [CrossRef]

278. Mestre, T.A.; Shah, B.B.; Connolly, B.S.; de Aquino, C.; Al Dhakeel, A.; Walsh, R.; Ghat, T.; Lui, J.P.; Fox, S.H. Famotidine, a Histamine H2 Receptor Antagonist, Does Not Reduce Levodopa-Induced Dyskinesia in Parkinson’s Disease: A Proof-of-Concept Study. Mov. Disord. Clin. Pract. 2014, 1, 219–224. [CrossRef]

279. Doi, H.; Sakakibara, R.; Sato, M.; Hirai, S.; Masaka, T.; Kishi, M.; Tsuyusaki, Y.; Tateno, A.; Tateno, F.; Takahashi, O.; et al. Nizatidine Ameliorates Gastroparesis in Parkinson’s Disease: A Pilot Study. Mov. Disord. 2014, 29, 562–566. [CrossRef] [PubMed]

280. Sakakibara, R.; Doi, H.; Sato, M.; Hirai, S.; Masaka, T.; Kishi, M.; Tsuyusaki, Y.; Tateno, A.; Tateno, F.; Aiba, Y.; et al. Nizatidine Ameliorates Slow Transit Constipation in Parkinson’s Disease. J. Am. Geriatr. Soc. 2015, 63, 399–401. [CrossRef] [PubMed]

281. Ferrada, C.; Ferre, S.; Casado, V.; Cortes, A.; Justinova, Z.; Barnes, C.; Canela, E.I.; Goldberg, S.R.; Leurs, R.; Lluis, C.; et al. Interactions between Histamine H3 and Dopamine D2 Receptors and the Implications for Striatal Function. Neuropharmacology 2008, 55, 190–197. [CrossRef]

282. Masini, D.; Lopes-Aguia, C.; Bonito-Oliva, A.; Papadia, D.; Anderssson, R.; Fisahn, A.; Fisone, G. The Histamine H3 Receptor Antagonist Thioperamide Rescues Circadian Rhythm and Memory Function in Experimental Parkinsonism. Transl. Psychiatry 2017, 7, e1088. [CrossRef]

283. Shan, L.; Bossers, K.; Luchetti, S.; Balesar, R.; Lethbridge, N.; Chazot, P.L.; Bao, A.M.; Swaab, D.F. Alterations in the Histaminergic System in the Substantia Nigra and Striatum of Parkinson’s Patients: A Postmortem Study. Neurobiol. Aging 2012, 33, 1488.e1–1488.e13. [CrossRef]

284. Zhou, P.; Homberg, J.R.; Fang, Q.; Wang, J.; Li, W.; Meng, X.; Shen, J.; Luan, Y.; Liao, P.; Swaab, D.F.; et al. Histamine-4 Receptor Antagonist [NI]777120 Inhibits Pro-Inflammatory Microglia and Prevents the Progression of Parkinson-Like Pathology and Behaviour in a Rat Model. Brain. Behav. Immun. 2019, 76, 61–73. [CrossRef]

285. Bordia, T.; Perez, X.A. Cholinergic Control of Striatal Neurons to Modulate L-Dopa-Induced Dyskinesias. Eur. J. Neurosci. 2019, 49, 859–868. [CrossRef]

286. Conti, M.M.; Chambers, N.; Bishop, C. A New Outlook on Cholinergic Interneurons in Parkinson’s Disease and L-DOPA-Induced Dyskinesia. Neurosci. Biobehav. Rev. 2018, 92, 67–82. [CrossRef]

287. Perez, X.A.; Bordia, T.; Quik, M. The Striatal Cholinergic System in L-Dopa-Induced Dyskinesias. J. Neural Transm. 2018, 125, 1251–1262. [CrossRef]

288. Freitas, M.E.; Fox, S.H. Nondopaminergic Treatments for Parkinson’s Disease: Current and Future Prospects. Neurodegener. Dis. Manag. 2016, 6, 249–268. [CrossRef]

289. Zhang, H.; Bai, L.; He, J.; Zhong, L.; Duan, X.; Ouyang, L.; Zhu, Y.; Wang, T.; Zhang, Y.; Shi, J. Recent Advances in Discovery and Development of Natural Products As source for Anti-Parkinson’s Disease Lead Compounds. Eur. J. Med. Chem. 2017, 141, 257–272. [CrossRef]

290. Montastruc, J.L.; Llu, M.E.; Rascol, O.; Senard, J.M. Drug-Induced Parkinsonism: A Review. Fund. Clin. Pharmacol. 1994, 8, 293–306. [CrossRef]

291. Brocks, D.R. Anticholinergic Drugs Used in Parkinson’s Disease: An Overlooked Class of Drugs from a Pharmacokinetic Perspective. J. Pharm. Pharm. Sci. 1999, 2, 39–46.
312. Huang, L.Z.; Grady, S.R.; Quik, M. Nicotine Reduces L-DOPA-Induced Dyskinesias by Acting at Beta2 Nicotinic Receptors. *J. Pharmacol. Exp. Ther.* 2011, 338, 932–941. [CrossRef] [PubMed]

313. Quik, M.; Campos, C.; Bordia, T.; Strachan, J.P.; Zhang, J.; McIntosh, J.M.; Letchworth, S.; Jordan, K. Alpha4beta2 Nicotinic Receptors Play a Role in the nAChR-Mediated Decline in L-Dopa-Induced Dyskinesias in Parkinsonian Rats. *Neuropsychopharmacology* 2013, 71, 191–203. [CrossRef]

314. Quik, M.; Campos, C.; Grady, S.R. Multiple Cns Nicotinic Receptors Mediate L-Dopa-Induced Dyskinesias: Studies with Parkinsonian Nicotinic Receptor Knockout Mice. *Biochem. Pharmacol.* 2013, 86, 1153–1162. [CrossRef]

315. Quik, M.; Park, K.M.; Hrachova, M.; Mallela, A.; Huang, L.Z.; McIntosh, J.M.; Grady, S.R. Role for Alpha6 Nicotinic Receptors in L-Dopa-Induced Dyskinesias in Parkinsonian Mice. *Neuropsychopharmacology* 2012, 63, 450–459. [CrossRef]

316. Quik, M.; Zhang, D.; Perez, X.A.; Bordia, T. Role for the Nicotinic Cholinergic System in Movement Disorders; Therapeutic Implications. *Pharmacol. Ther.* 2014, 144, 50–59. [CrossRef]

317. Barreto, G.E.; Iarkov, A.; Moran, V.E. Beneficial Effects of Nicotine, Cotinine and Its Metabolites as Potential Agents for Parkinson’s Disease. *Front. Aging Neurosci.* 2014, 6, 340.

318. Quik, M.; Bordia, T.; Zhang, D.; Perez, X.A. Nicotine and Nicotinic Receptor Drugs: Potential for Parkinson’s Disease and Drug-Induced Movement Disorders. *Int. Rev. Neurobiol.* 2015, 124, 247–271.

319. Leino, S.; Koski, S.K.; Rannanpää, S.; Salminen, O. Effects of Antidyskinetic Nicotine Treatment on Dopamine Release in Dorsal and Ventral Striatum. *Neurosci. Lett.* 2018, 672, 40–45. [CrossRef]

320. Zhang, D.; McGregor, M.; Bordia, T.; Perez, X.A.; McIntosh, J.M.; Decker, M.W.; Quik, M. A7 Nicotinic Receptor Agonists Reduce Levodopa-Induced Dyskinesias with Severe Nigrostriatal Damage. *Mov. Disord.* 2015, 30, 1901–1911. [CrossRef]

321. Zhang, D.; McGregor, M.; Decker, M.W.; Quik, M. The Alpha7 Nicotinic Receptor Agonist ABT-107 Decreases L-Dopa-Induced Dyskinesias in Parkinsonian Monkeys. *J. Pharmacol. Exp. Ther.* 2014, 351, 25–32. [CrossRef]

322. Zhang, D.; McGregor, M.; Bordia, T.; Perez, X.A.; McIntosh, J.M.; Decker, M.W.; Quik, M. A7 Nicotinic Receptor Agonists Reduce Levodopa-Induced Dyskinesias in Parkinsonian Monkeys. *Parkinsonism Relat. Disord.* 2014, 20, 1119–1123. [CrossRef]

323. Barreto, G.E.; Iarkov, A.; Moran, V.E. Beneficial Effects of Nicotine, Cotinine and Its Metabolites as Potential Agents for Parkinson’s Disease. *Front. Aging Neurosci.* 2014, 6, 340.

324. Di Paolo, T.; Grégoire, L.; Feuerbach, D.; Elbast, W.; Weiss, M.; Gomez-Mancilla, B. AQW051, a Novel and Selective Nicotinic Acetylcholine Receptor a7 Partial Agonist, Reduces L-Dopa-Induced Dyskinesias and Extends the Duration of L-Dopa Effects in Parkinsonian Monkeys. *Parkinsonism Relat. Disord.* 2014, 20, 508–517. [CrossRef]

325. Leino, S.; Koski, S.K.; Rannanpää, S.; Salminen, O. Attenuated Dopaminergic Neurodegeneration and Motor Dysfunction in Hemiparkinsonian Mice Lacking the Alpha5 Nicotinic Acetylcholine Receptor Subunit. *Neuropsychopharmacology* 2018, 138, 371–380. [CrossRef]

326. Thornton, E.; Hassall, M.M.; Corrigan, F.; Vink, R. The Nk1 Receptor Agonist N-Acetyl-L-Tryptophan Reduces Dyskinesia in a Hemi-Parkinsonian Rodent Model. *Parkinsonism Relat. Disord.* 2014, 20, 508–513. [CrossRef]
333. Mabrouk, O.S. Delta Opioid Pharmacology in Parkinson’s Disease. In *Delta Opioid Receptor Pharmacology and Therapeutic Applications*; Jutkiewicz, E.M., Ed.; Springer International Publishing: Cham, Switzerland, 2018. [CrossRef]

334. Huang, J.-Z.; Ren, Y.; Xu, Y.; Chen, T.; Xia, T.C.; Li, Z.-R.; Zhao, J.-N.; Hua, F.; Sheng, S.-Y.; Xia, Y. The Delta-Opioid Receptor and Parkinson’s Disease. *CNS Neurosci. Ther.* 2018, 24, 1089–1099. [CrossRef]

335. Sgroi, S.; Tonini, R. Opioidergic Modulation of Striatal Circuits, Implications in Parkinson’s Disease and Levodopa Induced Dyskinesia. *Front. Neurol.* 2018, 9, 524. [CrossRef]

336. Freo, U.; Furnari, M.; Ori, C. Effects of Tapentadol on Pain, Motor Symptoms and Cognitive Functions in Parkinson’s Disease. *J. Pain Res.* 2018, 11, 1849–1856. [CrossRef]

337. Henry, B.; Fox, S.H.; Crossman, A.R.; Brotchie, J.M. Mu- and Delta-Opioid Receptor Antagonists Reduce Levodopa-Induced Dyskinesia in the MPTP-Lesioned Primate Model of Parkinson’s Disease. *Expert. Neurol.* 2001, 171, 139–146. [CrossRef]

338. Koprich, J.B.; Fox, S.H.; Johnston, T.H.; Goodman, A.; Le Bourdonnec, B.; Dolle, R.E.; DeHaven, R.N.; DeHaven-Hudkins, D.L.; Little, P.J.; Brotchie, J.M. The Selective Mu-Opioid Receptor Antagonist Adl5510 Reduces Levodopa-Induced Dyskinesia without Affecting Antiparkinsonian Action in MPTP-Lesioned Macaque Model of Parkinson’s Disease. *Mov. Disord.* 2011, 26, 1225–1233. [CrossRef]

339. Billet, F; Costentin, J.; Dourmap, N. Influence of Corticostriatal Delta-Opioid Receptors on Abnormal Involuntary Movements Induced by L-DOPA in Hemiparkinsonian Rats. *Exp. Neurol.* 2012, 236, 339–350. [CrossRef]

340. Hudzik, T.J.; Howell, A.; Payza, K.; Cross, A.J. Antiparkinson Potential of Delta-Opioid Receptor Agonists. *Eur. J. Pharmacol.* 2000, 396, 101–107. [CrossRef]

341. Nozaki, C.; Le Bourdonnec, B.; Reiss, D.; Windh, R.T.; Little, P.J.; Dolle, R.E.; Kieffer, B.L.; Gaveraux-Ruff, C. Delta-Opioid Mechanisms for Adl5747 and ADL5859 Effects in Mice: Analgesia, Locomotion, and Receptor Internalization. *J. Pharmacol. Exp. Ther.* 2012, 342, 799–807. [CrossRef]

342. Spina, L.; Longoni, R.; Mulas, A.; Chang, K.J.; Di Chiara, G. Dopamine-Dependent Behavioural Stimulation by Non-Peptide Delta Opioids BW373U86 and SNC 80: 1. Locomotion, Rearing and Stereotypies in Intact Rats. *Behav. Pharmacol.* 1998, 9, 1–8.

343. Cox, H.; Togasaki, D.M.; Chen, L.; Langston, J.W.; Di Monte, D.A.; Quik, M. The Selective Kappa-Opioid Receptor Agonist U50,488 Reduces L-Dopa-Induced Dyskinesias but Worsens Parkinsonism in MPTP-Treated Primates. *Exp. Neurol.* 2007, 205, 101–107. [CrossRef]

344. Potts, L.E.; Park, E.S.; Woo, J.M.; Dyavar Shetty, B.L.; Singh, A.; Braithwaite, S.P.; Voronkov, M.; Papa, S.M.; Mouradian, M.M. Dual K-Agonist/M-Antagonist Opioid Receptor Modulation Reduces Levodopa-Induced Dyskinesia and Corrects Dysregulated Striatal Changes in the Nonhuman Primate Model of Parkinson Disease. *Ann. Neurol.* 2015, 77, 930–941. [CrossRef]

345. Klintenberg, R.; Svenningsson, P.; Gunne, L.; Andren, P.E. Naloxone Reduces Levodopa-Induced Dyskinesias and Apomorphine-Induced Rotations in Primate Models of Parkinsonism. *J. Neural Transm.* 2002, 109, 1295–1307. [CrossRef]

346. Fox, S.; Silverdale, M.; Kellett, M.; Davies, R.; Steiger, M.; Fletcher, N.; Crossman, A.; Brotchie, J. Non-Subtype-Selective Opioid Receptor Antagonism in Treatment of Levodopa-Induced Motor Complications in Parkinson’s Disease. *Mov. Disord.* 2004, 19, 554–560. [CrossRef]

347. Gomez-Mancilla, B.; Bedard, P.J. Effect of Nondopaminergic Drugs on L-Dopa-Induced Dyskinesias in MPTP-Treated Monkeys. *Clin. Neuropharmacol.* 1993, 16, 418–427. [CrossRef][PubMed]

348. Johnston, T.H.; Versi, E.; Howson, P.A.; Ravenscroft, P.; Fox, S.H.; Hill, M.P.; Reidenberg, B.E.; Corey, R.; Brotchie, J.M. DPI-289, a Novel Mixed Delta Opioid Agonist / Mu Opioid Antagonist (DAMA), Has L-DOPA-Sparing Potential in Parkinson’s Disease. *Neuropharmacology* 2018, 131, 116–127. [CrossRef][PubMed]

349. Lowery, J.J.; Raymond, T.J.; Giuelvis, D.; Bidlack, J.M.; Pilt, R.; Bilsky, E.J. In Vivo Characterization of MMP-2200, a Mixed Delta/Mu Opioid Agonist, in Mice. *J. Pharmacol. Exp. Ther.* 2011, 336, 767–778. [CrossRef][PubMed]

350. Su, T.P.; London, E.D.; Jaffe, J.H. Steroid Binding at Sigma Receptors Suggests a Link between Endocrine, Nervous, and Immune Systems. *Science* 1988, 240, 219–221. [CrossRef][PubMed]

351. Konitsiotis, S. Novel Pharmacological Strategies for Motor Complications in Parkinson’s Disease. *Expert Opin. Investig. Drugs* 2005, 14, 377–392. [CrossRef]
352. Mishina, M.; Ishiwata, K.; Ishii, K.; Kitamura, S.; Kimura, Y.; Kawamura, K.; Oda, K.; Sasaki, T.; Sakayori, O.; Hamamoto, M.; et al. Function of Sigma1 Receptors in Parkinson’s Disease. Acta Neurol. Scand. 2005, 112, 103–107. [CrossRef]

353. Francardo, V.; Bez, F.; Wieloch, T.; Nissbrandt, H.; Ruscher, K.; Cenci, M.A. Pharmacological Stimulation of Sigma-1 Receptors Has Neurorestorative Effects in Experimental Parkinsonism. Brain 2014, 137, 1998–2014. [CrossRef]

354. Paquette, M.A.; Foley, K.; Brudney, E.G.; Meshul, C.K.; Johnson, S.W.; Berger, S.P. The Sigma-1 Antagonist Bmy-14802 Inhibits L-DOPA-Induced Abnormal Involuntary Movements by a Way-100635-Sensitive Mechanism. Psychopharmacology 2009, 204, 743–754. [CrossRef]

355. Tsai, S.Y.; Pokrass, M.J.; Klauer, N.R.; De Credico, N.E.; Su, T.P. Sigma-1 Receptor Chaperones in Neurodegenerative and Psychiatric Disorders. Expert Opin. Ther. Targets 2014, 18, 1461–1476. [CrossRef]

356. Verhagen-Metman, L.; Blanchet, P.J.; van den Munckhof, P.; Del Dotto, P.; Natté, R.; Chase, T.N. A Trial of Dextromethorphan in Parkinsonian Patients with Motor Response Complications. Mov. Disord. 1998, 13, 414–417. [CrossRef]

357. Fox, S.H.; Metman, L.V.; Nutt, J.G.; Brodsky, M.; Factor, S.A.; Lang, A.E.; Pope, L.E.; Knowles, N.; Siffert, J. Trial of Dextromethorphan/Quinidine to Treat Levodopa-Induced Dyskinesia in Parkinson’s Disease. Mov. Disord. 2017, 32, 893–903. [CrossRef]

358. Johnston, T.H.; Geva, M.; Steiner, L.; Orbach, A.; Papapetropoulos, S.; Savola, J.M.; Reynolds, I.J.; Ravenscroft, P.; Hill, M.; Fox, S.H.; et al. Pridopidine, a Clinic-Ready Compound, Reduces 3,4-Dihydroxyphenylalanine-Induced Dyskinesia in Parkinsonian Macaques. Mov. Disord. 2018. [CrossRef]

359. Parkinson, J. An Essay on the Shaking Palsy. 1817. J. Neuropsychiatry. Clin. Neurosci. 2002, 14, 223–236, discussion 222. [CrossRef]

360. Schaeffer, E.; Pilotto, A.; Berg, D. Pharmacological Strategies for the Management of Levodopa-Induced Dyskinesia in Patients with Parkinson’s Disease. CNS Drugs 2014, 28, 1155–1184. [CrossRef]