

Minireviews

Predictive Value of Parkinsonian Primates in Pharmacologic Studies: A Comparison between the Macaque, Marmoset, and Squirrel Monkey^[S]

Nicolas Veyres, Adjia Hamadjida, and Philippe Huot

Centre de Recherche du Centre Hospitalier de l'Université de Montréal (N.V.), Montreal Neurological Institute (A.H., P.H.), and Department of Neurology and Neurosurgery, McGill University (P.H.), Montreal, Quebec, Canada

Received December 13, 2017; accepted March 6, 2018

ABSTRACT

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate is the gold-standard animal model of Parkinson disease (PD) and has been used to assess the effectiveness of experimental drugs on dyskinesia, parkinsonism, and psychosis. Three species have been used in most studies—the macaque, marmoset, and squirrel monkey—the last much less so than the first two species; however, the predictive value of each species at forecasting clinical efficacy, or lack thereof, is poorly documented. Here, we have reviewed all the published literature detailing pharmacologic studies that assessed the effects of experimental drugs on dyskinesia, parkinsonism, and psychosis in each of these species and have calculated their predictive value of success and failure at the clinical level. We found that, for dyskinesia, the macaque has a positive

predictive value of 87.5% and a false-positive rate of 38.1%, whereas the marmoset has a positive predictive value of 76.9% and a false-positive rate of 15.6%. For parkinsonism, the macaque has a positive predictive value of 68.2% and a false-positive rate of 44.4%, whereas the marmoset has a positive predictive value of 86.9% and a false-positive rate of 41.7%. No drug that alleviates psychosis in the clinic has shown efficacy at doing so in the macaque, whereas the marmoset has 100% positive predictive value. The small number of studies conducted in the squirrel monkey precluded us from calculating its predictive efficacy. We hope our results will help in the design of pharmacologic experiments and will facilitate the drug discovery and development process in PD.

Introduction

Since its accidental discovery (Davis et al., 1979; Langston et al., 1983), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been used extensively to model Parkinson disease (PD) in a breadth of nonhuman primates, enabling the investigation of anatomic (Jan et al., 2000; Zeng et al., 2008), behavioral (Pessiglione et al., 2004a,b), neurochemical (Soghomonian et al., 1994; Huot et al., 2008), and other aspects of the disease. The MPTP-lesioned primate has also been invaluable in the search for effective antidyskinetic and antiparkinsonian agents. A review article previously examined the translational predictive value of the MPTP-lesioned primate for the development of antidyskinetic drugs, but it was published more than a decade ago (Fox et al., 2006a), and many drugs have since been tested both in the primate and in clinical settings. This previous review did not examine the translational predictive value of the MPTP-lesioned

primate when it relates to the effect of drugs on parkinsonian disability or dopaminergic psychosis, nor did it look at differences between different primate species when it comes to predicting the clinical effectiveness of an experimental molecule.

We have therefore conducted a thorough and unbiased review of the literature to compare the predictive effectiveness of different MPTP-lesioned primate species on the clinical effectiveness of potential antidyskinetic, antiparkinsonian and antipsychotic agents.

We believe this review comes at a critical time given that it has recently been suggested that some primate species might be more suited than others to conduct behavioral pharmacologic research (Porrás et al., 2012); also, there have been several failures of high-profile drugs in clinical trials (Cook et al., 2014; Bernal et al., 2016), emphasizing the need to use the best animal model possible in preclinical settings to maximize chances of success when translating to the clinic.

Materials and Methods

Three nonhuman primate species have been used in most experiments to determine the antidyskinetic, antiparkinsonian, and antipsychotic

P.H. holds research support from Parkinson Canada, Fonds de Recherche Québec – Santé, Natural Sciences and Engineering Research Council of Canada, and the Weston Brain Institute.
<https://doi.org/10.1124/jpet.117.247171>.

[S] This article has supplemental material available at jpet.aspetjournals.org.

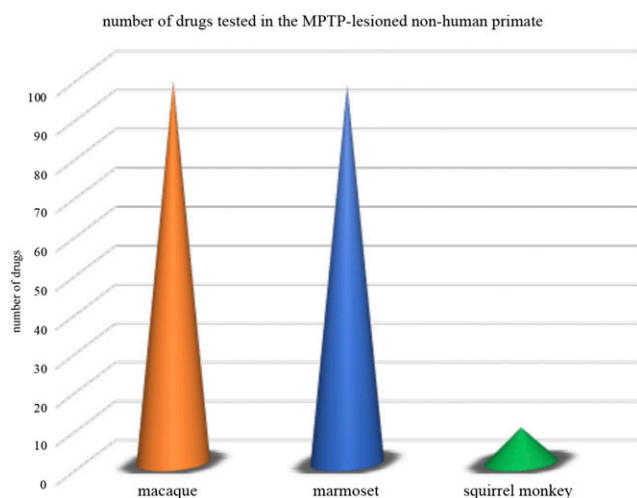


Fig. 1. A total of 98 experimental drugs were tested in the MPTP-lesioned macaque, 97 in the MPTP-lesioned marmoset, and nine in the MPTP-lesioned squirrel monkey.

effect of experimental drugs: the macaque [both cynomolgus (Di Paolo et al., 1986) and rhesus (Burns et al., 1983), *Macaca fascicularis* and *Macaca mulatta*, respectively], the common marmoset (Jenner et al., 1984) (*Callithrix jacchus*), and the common squirrel monkey (Langston et al., 1984) (*Saimiri sciureus*). For each of these three primate species, we have reviewed all the studies that reported their effect, or lack thereof, on dyskinesia, parkinsonism, and psychosis. We then sought which of these drugs tested in the nonhuman primate underwent clinical testing and compared their preclinical and clinical effects and calculated different predictive values (see *Endpoints*).

Inclusion Criteria. The literature search spans from 1983, when the first MPTP-lesioned nonhuman primate was engineered (Burns et al., 1983), until December 10, 2017. Studies published after this date, either online or in print format, are not included.

Only drugs whose preclinical and clinical efficacy, or lack thereof, were reported in peer-reviewed articles are included in this article. Results disseminated solely through abstracts or conference proceedings are therefore not reported here. We are aware that not all studies conducted on parkinsonian primates have been published and that the results of some clinical trials have not been disseminated through peer-reviewed journals; by choosing to include only studies and reports that were published in peer-reviewed journals, we may be introducing a selection bias in our analysis. For instance, although it has been studied in humans (NCT00034814, NCT00108667), the clinical effectiveness of talampanel will not be discussed here, as the results of the clinical trials where it was assessed were not published in peer-reviewed scientific journals. In addition, we have excluded L-3,4-dihydroxyphenylalanine (L-DOPA) and inhibitors of L-aromatic amino acid decarboxylase [e.g., benserazide (Rinne et al., 1975) and carbidopa (Marsden et al., 1973)] from our analysis, as these were used in almost all studies cited here to reverse parkinsonism and induce dyskinesia.

Research Methods. Literature review was conducted primarily through the United States National Library of Medicine database, accessed via PubMed. The search engine Google was used to complete the literature review and to access articles not indexed in the National Library of Medicine database. The following terms were used to perform the literature search: abnormal involuntary movements, chorea, cynomolgus, dyskinesia, dyskinetic, dystonia, hallucinations, hyperactivity, hyperkinesia, L-DOPA, levodopa, macaque, marmoset, monkey, MPTP, nonhuman primate, PD, parkinsonian, parkinsonism, primate, psychosis, rhesus, squirrel monkey, visual hallucinations.

Definition of Efficacy. Throughout our literature search, a reduction in dyskinesia/psychosis was considered to have occurred only if statistical significance was reached; trends were not

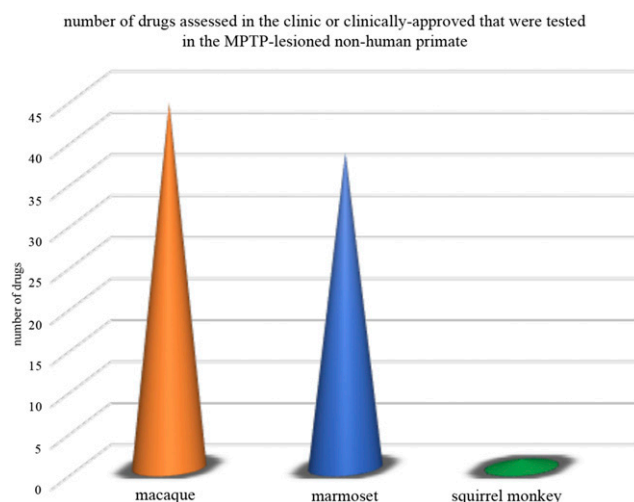


Fig. 2. A total of 44 drugs that are either clinically approved or that underwent clinical testing in PD were tested in the MPTP-lesioned macaque, 38 in the MPTP-lesioned marmoset, and one in the MPTP-lesioned squirrel monkey.

considered. A drug was considered to have antiparkinsonian benefit if it alleviated parkinsonism as monotherapy or as an adjunct to L-DOPA. Impulse-control disorders (Weintraub et al., 2010) were not considered a psychotic manifestation.

Several studies, especially in the macaque, were performed that administered drugs (e.g., cabergoline) to reduce the development of dyskinesia and then conducted postmortem experiments; we have included these studies in our analysis, even if their primary endpoint was not determination of pharmacologic efficacy. Studies reporting the effects of experimental drugs on rotational behavior in the hemi-MPTP-lesioned primate (e.g., Vermeulen et al., 1995) were not included.

In some instances, conflicting results were obtained with some drugs (e.g., studies encountered a therapeutic benefit), whereas others did not reach similar conclusions; whenever this happened, we calculated the predictive values using “best result” (i.e., the one that showed a therapeutic effect), weighing in the methods used in the studies (Gad, 2009), if applicable. For instance, in the case of preladenant, phase 2 studies have found antiparkinsonian efficacy (Hauser et al., 2011; Factor et al., 2013), whereas phase 3 studies did not (Hauser et al., 2015; Stocchi et al., 2017); but in one instance, the active comparator, rasagiline (Hauser et al., 2015), was also ineffective, despite proven antiparkinsonian benefit in randomized-controlled trials (Parkinson Study Group, 2005; Rascol et al., 2005), somewhat casting doubt on study conclusion. In this case, we considered that preladenant exerted antiparkinsonian benefit.

Endpoints. By comparing the outcomes of the primate studies on dyskinesia, parkinsonism, and psychosis, we have calculated, for each species, the positive predictive value, the negative predictive value, and the false-positive rate.

Here, we define the positive predictive value of a species as the percentage of cases for which a primate species has correctly predicted that an antidyskinetic or antiparkinsonian benefit would be achieved in the clinic. For the positive predictive value (eq. 1), the denominator was the number of drugs for which a therapeutic effect was achieved in the clinic, whereas the numerator was the number of these drugs that showed efficacy in the primate:

$$\frac{\text{number of molecules that showed effect in the primate}}{\text{number of clinically - effective molecules}} \quad (1)$$

Here, we define the negative predictive value of a species as the percentage of cases for which a primate species has correctly predicted that a lack of antidyskinetic or antiparkinsonian benefit

TABLE 1

Drugs tested in the MPTP-lesioned macaque

The number (*n*) of studies reporting the effect of each drug is in brackets.

Drug	Dyskinesia	Parkinsonism	Psychosis	References
17- α -Estradiol [<i>n</i> = 1]	ne	ne	na	Gomez-Mancilla and Bedard (1992b)
17- β -Estradiol [<i>n</i> = 2]	✓	✓	na	Gomez-Mancilla and Bedard (1992b), Bélanger et al. (2003a)
(-)-3-(3-Hydroxyphenyl)-N-n-propylpiperone [<i>n</i> = 1]	Ne	✓	na	Gomez-Mancilla and Bedard (1991)
(+)-4-Propyl-9-hydroxynaphthoxazine [<i>n</i> = 7]	Ne	✓	na	Gomez-Mancilla and Bedard (1991, 1992a), Luquin et al. (1992, 1993b), Blanchet et al. (1993, 1994), Belluzzi et al. (1994)
(-)-OSU-6162 [<i>n</i> = 1]	✓	ne	na	Hadj Tahar et al. (2001)
5-MDOT [<i>n</i> = 1]	✓	de	na	Gomez-Mancilla and Bedard (1993)
8-OH-DPAT [<i>n</i> = 1]	✓	ne	na	Munoz et al. (2008)
A-77,636 [<i>n</i> = 2]		✓	na	Blanchet et al. (1993, 1996b)
A-86,929 [<i>n</i> = 1]		✓	na	Grondin et al. (1997)
ADL-5510 [<i>n</i> = 1]	✓		na	Koprach et al. (2011)
AFQ-056 [<i>n</i> = 1]	✓	✓	na	Grégoire et al. (2011)
Amantadine [<i>n</i> = 7]	✓	de	na	Blanchet et al. (1998), Bibbiani et al. (2005b), Rylander et al. (2010), Bezard et al. (2013b), Grégoire et al. (2013), Ko et al. (2014b), Shen et al. (2015)
Anpirtoline [<i>n</i> = 1]	✓	de	na	Bézar et al. (2013a)
Apomorphine [<i>n</i> = 8]	ne	✓	na	Filion et al. (1991), Luquin et al. (1993a), Akai et al. (1995), Blanchet et al. (1997), Doan et al. (1999), Silverdale et al. (2002), Bibbiani et al. (2003, 2005a)
AQW-051 [<i>n</i> = 1]	✓	✓	na	Di Paolo et al. (2014)
Atropine [<i>n</i> = 1]	ne	✓	na	Gomez-Mancilla et al. (1991)
Baclofen [<i>n</i> = 1]	ne	de	na	Gomez-Mancilla and Bedard (1993)
BP-897 [<i>n</i> = 1]	✓	ne	na	Bézar et al. (2003)
Bromocriptine [<i>n</i> = 9]	ne	✓	na	Bédard et al. (1986), Falardeau et al. (1988), Gagnon et al. (1990, 1995), Rouillard et al. (1990), Gomez-Mancilla and Bedard (1991), Blanchet et al. (1993), Gomez-Mancilla et al. (1993), Belluzzi et al. (1994)
Cabergoline [<i>n</i> = 20]	ne	✓	na	Grondin et al. (1996), Morissette et al. (1998, 1999, 2010), Calon et al. (1999, 2000, 2002), Goulet et al. (1999, 2000), Hadj Tahar et al. (2000b), Bélanger et al. (2003b), Samadi et al. (2008a,b,c, 2010), Ouattara et al. (2009, 2010, 2011), Riahi et al. (2011)
CE [= 1]	ne	✓	na	Cao et al. (2007)
Citalopram [<i>n</i> = 1]	✓	de	na	Fidalgo et al. (2015)
CI-1041 [<i>n</i> = 14]	✓	ne	na	Hadj Tahar et al. (2004), Morissette et al. (2006a,b, 2010), Samadi et al. (2008a,b,c, 2010), Ouattara et al. (2009, 2010, 2011), Tamim et al. (2010), Riahi et al. (2011)
Clonidine [<i>n</i> = 2]	✓	✓	na	Gomez-Mancilla et al. (1991), Gomez-Mancilla and Bedard (1993)
Clozapine [<i>n</i> = 1]	✓	ne	na	Grondin et al. (1999b)
CLR-151 [<i>n</i> = 1]	✓	de	✓	Koprach et al. (2013)
Co-101,244/PD-174,494 [<i>n</i> = 1]	✓	ne	na	Blanchet et al. (1999)
CP-94,253 [<i>n</i> = 1]	ne	ne	na	Munoz et al. (2008)
CP-101,606 [<i>n</i> = 1]	ne	✓	na	Steece-Collier et al. (2000)
CX-516 [<i>n</i> = 1]	de	ne	na	Konitsiotis et al. (2000)
CY-208,243 [<i>n</i> = 8]	ne	✓	na	Gomez-Mancilla and Bedard (1991, 1992a), Gomez-Mancilla et al. (1992a, 1993), Blanchet et al. (1993), Gagnon et al. (1993, 1995), Luquin et al. (1993b)
DHEA [<i>n</i> = 2]	ne	✓	na	Bélanger et al. (2003a, 2006)
Diazepam [<i>n</i> = 1]	✓	ne	na	Gomez-Mancilla and Bedard (1993)
Dipraglurant [<i>n</i> = 1]	✓	ne	na	Bezard et al. (2014)
Docosahexaenoic acid [<i>n</i> = 5]	✓	ne	na	Samadi et al. (2006), Mahmoudi et al. (2009), Tamim et al. (2010), Riahi et al. (2012), Grégoire et al. (2015)
Eltoprazine [<i>n</i> = 3]	✓	de	na	Bezard et al. (2013b), Pinna et al. (2016), Ko et al. (2017)
Entacapone [<i>n</i> = 1]	ne	✓	na	Huot et al. (2013)
Ethosuximide [<i>n</i> = 1]	ne	✓	na	Gomez-Mancilla et al. (1992b)
F-15,599 [<i>n</i> = 1]	✓	ne	na	Huot et al. (2015b)
Famotidine [<i>n</i> = 1]	✓	✓	na	Johnston et al. (2010d)
Fenobam [<i>n</i> = 2]	✓	✓	na	Rylander et al. (2010), Ko et al. (2014b)
Fipamezole [<i>n</i> = 1]	✓	✓	na	Johnston et al. (2010c)
GYKI-47,261 [<i>n</i> = 1]	✓	ne	na	Bibbiani et al. (2005b)
Idazoxan [<i>n</i> = 2]	✓	✓	na	Bezard et al. (1999), Grondin et al. (2000)
Istradefylline [<i>n</i> = 3]	ne/de	✓	na	Grondin et al. (1999a), Bibbiani et al. (2003, Ko et al. (2016)
JL-18 [<i>n</i> = 1]	✓	de	na	Hadj Tahar et al. (2000a)
L-745,870 [<i>n</i> = 1]	✓	ne	na	Huot et al. (2012b)
L-tryptophan [<i>n</i> = 1]	✓	de	na	Ko et al. (2014a)
Levetiracetam [<i>n</i> = 1]	✓	ne	na	Bezard et al. (2004)
LY-235,959 [<i>n</i> = 1]	✓	ne	na	Papa and Chase (1996)
MDL-100,453 [<i>n</i> = 1]	✓	ne	na	Blanchet et al. (1999)
Meperidine [<i>n</i> = 1]	✓	ne	na	Gomez-Mancilla and Bedard (1993)
Methysergide [<i>n</i> = 1]	✓	de	na	Gomez-Mancilla and Bedard (1993)

(continued)

TABLE 1—Continued

Drug	Dyskinesia	Parkinsonism	Psychosis	References
MK-801 [n = 1]	✓	de	na	Gomez-Mancilla and Bedard (1993)
ML-218 [n = 1]	ne	ne	na	Galvan et al. (2016)
Morphine [n = 2]	✓	✓	na	Samadi et al. (2004), Yan et al. (2014)
MPEP [n = 7]	✓	de	na	Morin et al. (2010, 2013a,b, 2015a,b), Morissette et al. (2016)
MTEP [n = 2]	✓	de	na	Johnston et al. (2010b), Morin et al. (2010)
Nafadotride [n = 1]	✓	de	na	Bézard et al. (2003)
Nalbuphine [n = 1]	✓	ne	na	Potts et al. (2015)
Naloxone [n = 2]	ne	ne	na	Gomez-Mancilla and Bedard (1993), Samadi et al. (2003)
Naltrexone [n = 5]	ne/de	ne	na	Samadi et al. (2003, 2005a,c), Tamim et al. (2010), Koprich et al. (2011)
NBQX [n = 2]	ne	✓	na	Klockgether et al. (1991), Luquin et al. (1993b)
NNC-01-112 [n = 1]	✓	de	na	Grondin et al. (1999b)
PAMQX [n = 1]	na	✓	na	Papa et al. (2004)
PD-128,907 [n = 1]	ne	✓	na	Blanchet et al. (1997)
Physostigmine [n = 1]	✓	de	na	Gomez-Mancilla and Bedard (1993)
Pimavanserin [n = 1]	✓	ne	na	Vanover et al. (2008)
Pioglitazone [n = 1]	✓	de	na	Huot et al. (2015a)
PPI-1011 [n = 1]	✓	ne	na	Grégoire et al. (2015)
Prazosin [n = 1]	ne	ne	na	Visanji et al. (2009b)
Preladenant [n = 3]	ne	✓	na	Hodgson et al. (2010), Pinna et al. (2016), Ko et al. (2017)
Progesterone [n = 1]	ne	ne	na	Gomez-Mancilla and Bedard (1992b)
Propranolol [n = 1]	✓	de	na	Gomez-Mancilla and Bedard (1993)
Quetiapine [n = 1]	✓	ne	na	Oh et al. (2002)
Quinpirole [n = 12]	ne	✓	na	Bédard and Boucher (1989), Gomez-Mancilla and Bedard (1991), Gomez-Mancilla et al. (1992a), Blanchet et al. (1993, 1994), Akai et al. (1995), Grondin et al. (1997), Samadi et al. (2003, 2004, 2005c), Bibbiani et al. (2005b), Hyacinthe et al. (2014)
Remacemide [n = 1]	ne	✓	na	Greenamyre et al. (1994)
Ro-61,8048 [n = 6]	✓	ne	na	Samadi et al. (2005b), Grégoire et al. (2008), Ouattara et al. (2009), Tamim et al. (2010), Riahi et al. (2012, 2013)
Ro 65-6570 [n = 1]	✓	ne	na	Marti et al. (2012)
Rotigotine [n = 2]	ne	✓	na	Belluzzi et al. (1994), Domino and Ni (1998a)
Safinamide [n = 1]	✓	✓	na	Grégoire et al. (2013)
Sarizotan [n = 2]	✓	de	na	Bibbiani et al. (2001), Grégoire et al. (2009)
SCH-23,390 [n = 3]	✓	de	na	Gomez-Mancilla and Bedard (1991), Akai et al. (1995), Grondin et al. (1999b)
Simvastatin [n = 1]	✓	ne	na	Tison et al. (2013)
SKF-38,393 [n = 6]	ne	✓/ne	na	Falardeau et al. (1988), Bédard and Boucher (1989), Gagnon et al. (1990), Rouillard et al. (1990), Blanchet et al. (1993), Hyacinthe et al. (2014)
SKF-82,958 [n = 18]	ne	✓	na	Blanchet et al. (1993, 1994, 1996a,b), Akai et al. (1995), Goulet et al. (1996, 1999), Domino and Ni (1998a), Morissette et al. (1998, 1999), Calon et al. (1999, 2000, 2002), Grondin et al. (1999c), Samadi et al. (2003, 2004, 2005c), Bibbiani et al. (2005b)
ST-198 [n = 1]	✓	de	na	Bézard et al. (2003)
Sulpiride [n = 3]	✓	de	na	Gomez-Mancilla and Bedard (1991), Akai et al. (1995), Grondin et al. (1999b)
Sumanitrole [n = 1]	ne	✓	na	McCall et al. (2005)
Talampanel [n = 1]	✓	✓	na	Konitsiotis et al. (2000)
Tamoxifen [n = 1]	✓	ne	na	Smith et al. (2007)
TC-8831 [n = 1]	✓	ne	na	Johnston et al. (2013b)
Terguride [n = 1]	ne	✓	na	Gomez-Mancilla and Bedard (1991)
Trihexyphenidyl [n = 2]	ne	✓	na	Domino and Ni (1998a,b)
U-91,356-A [n = 4]	ne	✓	na	Blanchet et al. (1995), Calon et al. (1995), Goulet et al. (1997), Morissette et al. (1997)
U-99,194-A [n = 1]	✓	ne	na	Blanchet et al. (1997)
VU-0,476,406 [n = 1]	✓	ne	na	Shen et al. (2015)
Yohimbine [n = 1]	✓	ne	na	Gomez-Mancilla and Bedard (1993)

de, deleterious; na, not assessed; ne, not effective; ✓, effective.

would be achieved in the clinic. For the negative predictive value (eq. 2), the denominator was the number of drugs for which a therapeutic effect was not achieved in the clinic, and the numerator was the number of these drugs that did not show efficacy in the primate:

$$\frac{\text{number of molecules that did not show effect in the primate}}{\text{number of clinically - ineffective molecules}} \quad (2)$$

Here, we define the false-positive rate of a species as the percentage of cases for which a primate species has incorrectly

$$\frac{\text{number of clinically-ineffective molecules that showed positive effect in the primate}}{\text{number of clinically-ineffective molecules}} \quad (3)$$

TABLE 2

Drugs tested in the MPTP-lesioned marmoset

The number (n) of studies reporting the effect of each drug is in brackets.

Drug	Dyskinesia	Parkinsonism	Psychosis	References
Δ -(9)-THC [n = 1]	ne	✓	na	van Vliet et al. (2008)
(+)-PHNO [n = 2]	ne	✓	na	Nomoto et al. (1987), Close et al. (1990)
(+)-N-n-propyl-3-(3-hydroxyphenyl)-piperidine [(+)-3PPP] [n = 1]	ne	✓	na	Close et al. (1990)
(-)-N-n-propyl-3-(3-hydroxyphenyl)-piperidine (-)-3PPP [n = 1]	ne	ne	Na	Close et al. (1990)
(-)-N-0437 [n = 1]	ne	✓	na	Löschmann et al. (1989)
(-)-OSU-6162 [n = 1]	✓	ne	na	Ekesbo et al. (1997)
2-amino-5,6-dihydroxytetralin (N,N-dipropyl A-5,6-DTN) [n = 1]	ne	✓	na	Close et al. (1990)
R-(-)-11-OH-NPa [n = 1]	ne	✓	na	Lincoln et al. (2016)
A-66,359 [n = 1]	ne	de	na	Gnanalingham et al. (1995c)
A-77,636 [n = 4]	ne	✓	na	Kebabian et al. (1992), Pearce et al. (1995, 1999), Smith et al. (2002a)
A-86,929 [n = 3]	ne	✓	na	Shiosaki et al. (1996), Pearce et al. (1999), Treseder et al. (2000)
ABT-431 [n = 1]	ne	✓	na	Shiosaki et al. (1996)
Amantadine [n = 3]	✓	ne	de	Hill et al. (2004b), Visanji et al. (2006), Kobylecki et al. (2011)
Aplindore [n = 1]	ne	✓	na	Jackson et al. (2010)
Apomorphine [n = 6]	ne	✓	ne	Löschmann et al. (1992), Pearce et al. (1995), Fox et al. (2001), Maratos et al. (2003), Visanji et al. (2006), Lincoln et al. (2016)
Atropine [n = 2]	ne	✓	ne	Close et al. (1990), Jackson et al. (2014)
Benztropine [n = 1]	ne	✓	na	Close et al. (1990)
rasofensine [n = 1]	ne	✓	na	Pearce et al. (2002)
Bromocriptine [n = 3]	ne	✓	na	Close et al. (1990), Pearce et al. (1995, 1998)
BTS-74,398 [n = 2]	ne	✓/ne	na	Hansard et al. (2002b, 2004)
Bupropion [n = 2]	ne	✓/ne	na	Hansard et al. (2002b, 2011)
Clozapine [n = 1]	✓	ne	✓	Visanji et al. (2006)
CP-101,606 [n = 1]	ne	✓	na	Nash et al. (2004)
CPP [n = 1]	ne	✓	na	Löschmann et al. (1991)
CY-208,243 [n = 2]	ne	✓	na	Temlett et al. (1988, 1989)
Cyproheptadine [n = 1]	✓	ne	ne	Henry et al. (2001)
Entacapone [n = 4]	ne	✓	na	Smith et al. (1997, 2003, 2005), Zubair et al. (2007)
Fipamezole [n = 1]	✓	✓	na	Savola et al. (2003)
GBR-12,909 [n = 2]	ne	✓	na	Hansard et al. (2002a,b)
Haloperidol [n = 1]	✓	de	✓	Visanji et al. (2006)
Idazoxan [n = 1]	✓	✓	na	Henry et al. (1999)
IEM-1460 [n = 1]	✓	ne	na	Kobylecki et al. (2010)
ifenprodil [n = 1]	ne	✓	na	Nash et al. (2000)
Imetit [n = 1]	✓	ne	na	Gomez-Ramirez et al. (2006)
Immepip [n = 1]	✓	ne	na	Gomez-Ramirez et al. (2006)
Istradefylline [n = 6]	ne	✓	na	Kanda et al. (1998a,b, 2000), Uchida et al. (2014, 2015a,b)
J-113,397 [n = 1]	✓	ne	na	Visanji et al. (2008)
JNJ-27,063,699 [n = 1]	ne	✓	na	Philippens et al. (2014)
Levetiracetam [n = 3]	✓	ne	na	Hill et al. (2003, 2004a,b)
LY-141,865 [n = 1]	ne	✓	na	Nomoto et al. (1985)
MDMA [n = 1]	✓	✓	na	Iravani et al. (2003)
Melanocyte-inhibiting factor [n = 1]	ne	ne	na	Katzenschlager et al. (2007)
Mianserin [n = 1]	✓	de	✓	Hamadjida et al. (2018)
Mirtazapine [n = 1]	✓	ne	✓	Hamadjida et al. (2017)
Modafinil [n = 2]	ne	✓	na	Jenner et al. (2000), van Vliet et al. (2008)
N-0437 [n = 1]	ne	✓	na	Löschmann et al. (1989)
N-methyl scopolamine [n = 1]	ne	✓	na	Jackson et al. (2014)
Nabilone [n = 1]	✓	ne	na	Fox et al. (2002)
Naltrexone [n = 1]	✓	ne	na	Henry et al. (2001)
Naltrindole [N = 1]	✓	ne	na	Henry et al. (2001)
Neostigmine [n = 1]	ne	✓	na	Jackson et al. (2014)
Nisoxetine [n = 1]	ne	✓/de	na	Hansard et al. (2002b)
NBQX [n = 1]	ne	✓	na	Löschmann et al. (1991)
Nomifensine [n = 2]	ne	✓	na	Close et al. (1990), Hansard et al. (2002b)
Oxotremorine [n = 1]	ne	de	na	Jackson et al. (2014)
Pardoprunox [n = 3]	✓	✓	na	Johnston et al. (2010a), Jones et al. (2010), Tayarani-Binazir et al. (2010a)

(continued)

TABLE 2—Continued

Drug	Dyskinesia	Parkinsonism	Psychosis	References
Pergolide [<i>n</i> = 5]	ne	✓	na	Pearce et al. (1995), Maratos et al. (2003), Fox et al. (2006b), Uchida et al. (2015a,b)
Physostigmine [<i>n</i> = 1]	ne	de	na	Jackson et al. (2014)
Piribedil [<i>n</i> = 4]	ne	✓	na	Smith et al. (1996, 2000, 2002b, 2006)
Pramipexole [<i>n</i> = 4]	ne	✓	na	Iravani et al. (2003, 2006), Fox et al. (2006b), Tayarani-Binazir et al. (2010b)
Quetiapine [<i>n</i> = 1]	✓	ne	✓	Visanji et al. (2006)
Quinpirole [<i>n</i> = 8]	ne	✓	na	Nomoto et al. (1988), Close et al. (1990), Löschmann et al. (1992), Gnanalingham et al. (1995a,b), Pearce et al. (1995), Kanda et al. (2000), Treseder et al. (2000)
(<i>R</i>)-(+)-OHDPAT [<i>n</i> = 1]	✓	de	na	Iravani et al. (2006)
R-MDMA [<i>n</i> = 1]	✓	ne	✓	Huot et al. (2011)
Raclopride [<i>n</i> = 4]	✓	de	na	Löschmann et al. (1992), Gnanalingham et al. (1995c), Ekesbo et al. (1997), Smith et al. (2002a)
Rauwolscline [<i>n</i> = 1]	✓	ne	na	Henry et al. (1999)
RGFP-109 [<i>n</i> = 1]	✓	ne	na	Johnston et al. (2013a)
Rimonabant [<i>n</i> = 1]	✓	✓	na	van der Stelt et al. (2005)
Ro-25,6981 [<i>n</i> = 1]	ne	✓	na	Löschmann et al. (2004)
Ropinirole [<i>n</i> = 13]	ne	✓	na	Pearce et al. (1998), Maratos et al. (2001), Hill et al. (2003), Millan et al. (2004), Silverdale et al. (2004), Fox et al. (2006b), Jackson et al. (2007, 2010), Zubair et al. (2007), Stockwell et al. (2008), Johnston et al. (2010a), Uchida et al. (2015a,b)
Rotigotine [<i>n</i> = 3]	ne	✓	na	Rose et al. (2007), Stockwell et al. (2009, 2010)
S-32,504 [<i>n</i> = 2]	ne	✓	na	Millan et al. (2004), Hill et al. (2006)
S-33,084 [<i>n</i> = 3]	ne	✓	na	Silverdale et al. (2004), Hill et al. (2006), Visanji et al. (2009a)
S-MDMA [<i>n</i> = 1]	de	✓	ne	Huot et al. (2011)
S,S-hydroxybupropion [<i>n</i> = 1]	ne	✓	na	Hansard et al. (2011)
SB-224,289-A [<i>n</i> = 1]	ne	ne	na	Jackson et al. (2004)
SCH-23,390 [<i>n</i> = 4]	ne	de	na	(Temlett et al. (1988), Löschmann et al. (1992), Gnanalingham et al. (1995c), Smith et al. (2002a)
Scopolamine [<i>n</i> = 2]	ne	✓	na	Close et al. (1990), Jackson et al. (2014)
Sertraline [<i>n</i> = 1]	ne	de	na	Hansard et al. (2002b)
SKF-38,393 [<i>n</i> = 6]	ne	ne/de	na	Nomoto et al. (1985, 1988), Close et al. (1990), Löschmann et al. (1992), Gnanalingham et al. (1995a,b)
SKF-75,670 [<i>n</i> = 2]	ne	de	na	Gnanalingham et al. (1995a,b)
SKF-80,723 [<i>n</i> = 4]	ne	✓/de	na	Gnanalingham et al. (1995a,b,c), Kanda et al. (2000)
SKF-82,958 [<i>n</i> = 2]	ne	✓/de	na	Gnanalingham et al. (1995a,b)
SKF-83,565 [<i>n</i> = 1]	ne	✓	na	Gnanalingham et al. (1995a)
SKF-83,959 [<i>n</i> = 3]	ne	✓	na	Gnanalingham et al. (1995a,b,c)
SKF-99,101-H [<i>n</i> = 1]	✓	ne/de	na	Jackson et al. (2004)
SNC-80 [<i>n</i> = 1]	ne	✓	na	Hille et al. (2001)
ST-1535 [<i>n</i> = 1]	ne	✓	na	Rose et al. (2006)
Sulpiride [<i>n</i> = 2]	ne	de	na	Temlett et al. (1988), Jones et al. (2010)
Terguride [<i>n</i> = 1]	ne	✓	na	Lange et al. (1992)
Topiramate [<i>n</i> = 2]	✓	ne	na	Silverdale et al. (2005), Kobylecki et al. (2011)
Trihexyphenidyl [<i>n</i> = 1]	ne	✓	na	Jackson et al. (2014)
URB-597 [<i>n</i> = 1]	ne	ne	ne	Johnston et al. (2011)
UWA-101 [<i>n</i> = 2]	ne	✓	ne	Huot et al. (2012a), Johnston et al. (2012)
UWA-121 [<i>n</i> = 1]	ne	✓	ne	Huot et al. (2014)
UWA-122 [<i>n</i> = 1]	✓	✓	ne	Huot et al. (2014)
Yohimbine [<i>n</i> = 1]	✓	ne	na	Henry et al. (1999)

de, deleterious; na, not assessed; ne, not effective; ✓, effective.

predicted that a lack of antidyskinetic or antiparkinsonian benefit would be achieved in the clinic. For the false-positive rate (eq. 3), the denominator was the number of drugs for which a therapeutic effect was not achieved in the clinic; the numerator was the number of these clinically ineffective drugs that were deemed to be effective in the primate:

Results

Pharmacologic Targets

Several pharmacologic targets have been modulated in studies performed in the MPTP-lesioned macaque and the MPTP-lesioned marmoset. In contrast, only dopaminergic,

TABLE 3

Drugs tested in the MPTP-lesioned squirrel monkey

The number (*n*) of studies reporting the effect of each drug is in brackets.

Drug	Dyskinesia	Parkinsonism	Psychosis	References
ABT-089 [<i>n</i> = 1]	✓	ne	na	Zhang et al. (2014)
ABT-107 [<i>n</i> = 1]	✓	ne	na	Zhang et al. (2013)
ABT-126 [<i>n</i> = 1]	✓	ne	na	Zhang et al. (2015)
ABT-894 [<i>n</i> = 3]	✓	ne	na	Zhang et al. (2013, 2014, 2015)
BP-897 [<i>n</i> = 1]	✓	de	na	Hsu et al. (2004)
Nicotine [<i>n</i> = 4]	✓	ne	na	Quik et al. (2007, 2013a,b), Zhang et al. (2015)
TC-8831 [<i>n</i> = 1]	✓	ne	na	Zhang et al. (2013)
U50-488 [<i>n</i> = 1]	✓	de	na	Cox et al. (2007)
Varenicline [<i>n</i> = 1]	✓	ne	na	Zhang et al. (2013)

de, deleterious; na, not assessed; ne, not effective; ✓, effective.

opioidergic and cholinergic targets have been assessed in studies conducted in the MPTP-lesioned squirrel monkey (see Supplemental Table 1 for the pharmacologic profile of all molecules that have been tested in the MPTP-lesioned primate).

A total of 98 different molecules were assessed in the MPTP-lesioned macaque, 97 in the MPTP-lesioned marmoset, and nine in the MPTP-lesioned squirrel monkey (Fig. 1). Of all the molecules tested in the MPTP-lesioned primate, 64 have been assessed at the clinical level or are clinically approved. Of these, 44 were tested in the macaque, 38 in the marmoset, and one in the squirrel monkey (Fig. 2). Because very few drugs have been tested in the MPTP-lesioned squirrel monkey compared with the macaque and the marmoset, we do not discuss it further in the text, but we have nevertheless included it in the tables.

We have summarized our research results in tables:

- Table 1: drugs tested in the MPTP-lesioned macaque
- Table 2: drugs tested in the MPTP-lesioned marmoset
- Table 3: drugs tested in the MPTP-lesioned squirrel monkey
- Table 4: drugs tested in the MPTP-lesioned primate that were tested in the clinic or are clinically-available

In each table, the drugs are listed in numerical or alphabetical order.

We have also summarized our results in figures:

- Figure 1: number of drugs tested in the MPTP-lesioned nonhuman primate
- Figure 2: number of drugs assessed in the clinic or clinically approved that were tested in the MPTP-lesioned nonhuman primate
- Figure 3: antidyskinetic positive predictive value of the MPTP-lesioned nonhuman primate
- Figure 4: antidyskinetic negative predictive value of the MPTP-lesioned nonhuman primate
- Figure 5: antidyskinetic false positive rate of the MPTP-lesioned nonhuman primate
- Figure 6: antiparkinsonian positive predictive value of the MPTP-lesioned nonhuman primate
- Figure 7: antiparkinsonian negative predictive value of the MPTP-lesioned nonhuman primate
- Figure 8: antiparkinsonian false positive rate of the MPTP-lesioned nonhuman primate
- Figure 9: worsening of parkinsonism positive predictive value of the MPTP-lesioned nonhuman primate.

Prediction of Antidyskinetic Effect

Of the 64 drugs that were tested in the clinic and in the MPTP-lesioned primate, 22 showed antidyskinetic effect in clinical trials, no antidyskinetic effect was found or reported for 36 drugs, and four drugs showed a deleterious effect on dyskinesia severity (see Supplemental Table 2 for details).

MPTP-Lesioned Macaque. Of the 22 drugs that demonstrated an antidyskinetic effect in clinical settings, 16 were tested in the macaque, and an antidyskinetic effect was obtained with 14 (87.5% positive predictive value, Fig. 3). Of the 36 drugs for which no antidyskinetic effect was found or reported in the clinic, 21 were tested in the macaque. No antidyskinetic effect was encountered or reported with 13 (61.9% negative predictive efficacy, Fig. 4); an antidyskinetic action was found with eight (38.1% false-positive rate, Fig. 5). Of the four drugs that had a deleterious effect on dyskinesia severity in the clinic, two were tested in the macaque, and an exacerbation of dyskinesia could not be demonstrated in either case.

MPTP-Lesioned Marmoset. Of the 22 drugs that demonstrated an antidyskinetic effect in clinical settings, 13 were tested in the marmoset, and an antidyskinetic effect was obtained with 10 (76.9% positive predictive value, Fig. 3). Of the 36 drugs for which no antidyskinetic effect was found or reported, 22 were tested in the marmoset, and the absence of antidyskinetic effect was identified in 19 (86.4% negative predictive value, Fig. 4), whereas an antidyskinetic action was found with three (15.6% false-positive rates Fig. 5). Of the four drugs that had a deleterious effect on dyskinesia severity, three were tested in the marmoset, but an exacerbation of dyskinesia could not be demonstrated in any case.

Prediction of Antiparkinsonian Action

Of the 64 drugs that were tested in the clinic and in the MPTP-lesioned primate, 34 showed an antiparkinsonian effect in clinical trials; no antiparkinsonian effect was found or reported for 24 drugs, and five drugs were found to have a deleterious effect on parkinsonian disability (see Supplemental Table 3 for details).

MPTP-Lesioned Macaque. Of the 34 drugs that showed antiparkinsonian effect in clinical trials, 22 were tested in the macaque, and an antiparkinsonian benefit was obtained with 15 (68.2% positive predictive value, Fig. 6). Of the 24 drugs for which no antiparkinsonian effect was found or reported, 18 were tested in the macaque, and no antiparkinsonian effect was encountered or reported with six (33.3% negative predictive value, Fig. 7), whereas antiparkinsonian action was

TABLE 4

Drugs tested in the MPTP-lesioned primate that were tested in the clinic or are clinically available

Drug	Dyskinesia	Parkinsonism	Psychosis	References
(+)-4-Propyl-9-hydroxynaphthoxazine	Ne	✓	na	Stoessl et al. (1985), Grandas et al. (1987), Muentert et al. (1988)
ABT-431	Ne	✓	na	Rascol et al. (1999, 2001b)
AFQ-056	✓/ne	ne	na	Stocchi et al. (2013), Trenkwalder et al. (2016b)
Amantadine	✓	✓	na	Parkes et al. (1971), Butzer et al. (1975), Verhagen Metman et al. (1998), Luginer et al. (2000), Del Dotto et al. (2001), Oertel et al. (2017), Pahwa et al. (2017)
Apomorphine	ne	✓	na	Schwab et al. (1951), Corsini et al. (1979), Stibe et al. (1987)
AQW-051	ne	ne	na	Trenkwalder et al. (2016a)
Atropine	ne	✓	na	Boman and Meurman (1970)
Benzotropine	ne	✓	na	Doshay (1956)
Brasofensine	ne	ne	na	Frackiewicz et al. (2002)
Bromocriptine	ne	✓	na	Agid et al. (1979), Quinn et al. (1981), Jellinger (1982), Hely et al. (1994), Montastruc et al. (1994, Castro-Caldas et al. (2006)
Bupropion	ne	✓	na	Goetz et al. (1984)
Cabergoline	ne	✓	na	Ahlskog et al. (1996), Rinne et al. (1997), Deuschl et al. (2007)
Citalopram	✓	✓	na	Rampello et al. (2002), Pålhagen et al. (2008, 2009)
Clonidine	na	✓/de	na	Shoulson and Chase (1976), Serrano-Dueñas (2000)
Clozapine	✓	✓	✓	Durif et al. (1997, 2004); The French Clozapine Parkinson Study Group (1999), Parkinson Study Group (1999)
CP-101,606	✓	ne	na	Nutt et al. (2008)
CY-208,243	ne	✓	na	Tsui et al. (1989), Emre et al. (1992)
Diazepam	✓	✓	na	Pourcher et al. (1989)
Dipraglurant	✓	ne	na	Tison et al. (2016)
Eltoprazine	✓	ne	na	Svenningsson et al. (2015)
Entacapone	de	✓	na	Kaakkola et al. (1994), Merello et al. (1994), Fenelon et al. (2003)
Ethosuximide	ne	ne/de	na	Pourcher et al. (1992)
Famotidine	ne	ne	na	Molinari et al. (1995), Mestre et al. (2014)
Fipamezole	✓	ne	na	Lewitt et al. (2012)
Haloperidol	✓	de	na	Klawans and Weiner (1974)
Idazoxan	✓/ne	ne	na	Manson et al. (2000), Rascol et al. (2001a)
Istradefylline	ne	✓	na	Hauser et al. (2003, 2008), LeWitt et al. (2008), Pourcher et al. (2012)
L-tryptophan	ne	ne	na	Coppen et al. (1972)
Levetiracetam	✓/ne	ne	ne	Wolz et al. (2010), Stathis et al. (2011), Wong et al. (2011)
Melanocyte-inhibiting factor	ne	ne	na	Gerstenbrand et al. (1975)
Methysergide	ne	ne	na	Klawans and Ringel (1973)
Mianserin	na	na	✓	Ikeguchi and Kuroda (1995)
Mirtazapine	✓	✓	✓	Gordon et al. (2002), Meco et al. (2003), Nagata et al. (2013), Tagai et al. (2013)
Modafinil	ne	ne	na	Tyne et al. (2007, 2010)
Morphine	✓	de	na	Berg et al. (1999)
Nabilone	✓	ne	na	Sieradzan et al. (2001)
Naloxone	✓/ne	✓/ne	na	Trabucchi et al. (1982), Fox et al. (2004)
Naltrexone	✓/ne	ne	na	Rascol et al. (1994), Manson et al. (2001)
Nicotine	na	✓/ne	na	Vieregge et al. (2001), Lemay et al. (2004), Villafane et al. (2007)
Nomifensine	de	✓	na	Teychenne et al. (1976), Bedard et al. (1977), Park et al. (1977, 1981)
Pardoprunox	ne	✓	na	Bronzova et al. (2010), Sampaio et al. (2011), Rascol et al. (2012)
Pergolide	ne	✓	na	Lieberman et al. (1986), Wright et al. (1987), Olanow et al. (1994), Mizuno et al. (1995), Oertel et al. (2006)
Physostigmine	✓/ne	de	na	Tarsy et al. (1974), Lindeboom and Lakke (1978), Clough et al. (1984)
Pimavanserin	ne	ne	✓	Meltzer et al. (2010), Cummings et al. (2014)
Pioglitazone	ne	ne	na	NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators (2015)
Piribedil	ne	✓	na	Castro-Caldas et al. (2006), Rascol et al. (2006b)
Pramipexole	ne	✓	na	Lieberman et al. (1997), Parkinson Study Group (2000b), Poewe et al. (2007)
Preladenant	de	✓/ne	na	Hauser et al. (2011, 2015), Factor et al. (2013), Stocchi et al. (2017)
Propranolol	✓	✓/ne	na	Koller and Herberster (1987), Carpentier et al. (1996)
Quetiapine	✓/ne	ne/de	✓/ne	Fernandez et al. (1999), (2003), Baron and Dalton (2003), Katzenschlager et al. (2004), Ondo et al. (2005)
Remacemide	ne	ne	na	Parkinson Study Group (2000a, 2001), Shoulson et al. (2001)
Ropinirole	ne	✓	na	Rascol et al. (1996, 2000, 2006a), Korczyn et al. (1999)
Rotigotine	ne	✓	na	Parkinson Study Group (2003), Giladi et al. (2007), LeWitt et al. (2007), Mizuno et al. (2013)
Safinamide	✓	✓	na	Borghain et al. (2014a,b), Cattaneo et al. (2015), Schapira et al. (2017)
Sarizotan	ne	de	na	Olanow et al. (2004), Goetz et al. (2007, 2008)
Scopolamine	ne	✓	na	Gruchet (1952), Duvoisin (1967)
Sertraline	ne	ne	na	Hauser and Zesiewicz (1997), Antonini et al. (2006), Kulisevsky et al. (2008), Marino et al. (2008)
Simvastatin	ne	ne	na	Tison et al. (2013)
SKF-38,393	ne	ne	na	Braun et al. (1987)
Sulpiride	✓	de	na	Lees et al. (1978)
Sumanitrole	ne	✓/ne	na	Barone et al. (2007), Singer et al. (2007)

(continued)

TABLE 4—Continued

Drug	Dyskinesia	Parkinsonism	Psychosis	References
Terguride	ne	✓	na	Filipova et al. (1988), Martignoni et al. (1995)
Topiramate	ne/de	ne	na	Kobylecki et al. (2014), Goetz et al. (2017)
Trihexyphenidyl	ne	✓	na	Martin et al. (1974), Lamid and Jenkins (1975)
Yohimbine	ne	✓	na	Montastruc et al. (1981)

de, deleterious; na, not assessed; ne, not effective; ✓, effective.

found with eight (44.4% false-positive rate, Fig. 8). Of the five drugs that had a deleterious effect on parkinsonian disability, four were tested in the macaque, and this deleterious effect on parkinsonism was correctly identified in three (75% predictive value, Fig. 9).

MPTP-Lesioned Marmoset. Of the 34 drugs that showed antiparkinsonian effect in clinical trials, 23 were tested in the marmoset; an antiparkinsonian effect was obtained with 20 (86.9% positive predictive value, Fig. 6). Of these, 24 drugs did not find or did not report an antiparkinsonian effect, 12 were tested in the marmoset, and no antiparkinsonian effect was encountered with six (50.0% negative predictive value, Fig. 7), whereas antiparkinsonian benefit was found with five (41.7% false-positive rate, Fig. 8). Of the five drugs found to have a deleterious effect on parkinsonian disability, three were tested in the marmoset, all of which hindered parkinsonism (100% predictive value, Fig. 9).

Prediction of Antipsychotic Action

Of the 64 drugs that were tested in the clinic and in the MPTP-lesioned primate, five showed an antipsychotic effect in clinical trials/reports (clozapine, mianserin, mirtazapine, pimavanserin, quetiapine). Compared with dyskinesia and parkinsonism, the effect of experimental drugs on dopaminergic psychosis has been far less studied in the MPTP-lesioned

primate. No drug that underwent clinical testing or that is clinically available has demonstrated antipsychotic effect in the MPTP-lesioned macaque or the MPTP-lesioned squirrel monkey. Pimavanserin was not tested in the MPTP-lesioned marmoset, but an antipsychotic benefit was achieved with clozapine, mianserin, mirtazapine, and quetiapine (100% positive predictive value).

Discussion

Here, we have reviewed all the literature published in peer-reviewed scientific journals that reported the results of pharmacologic studies conducted in the MPTP-lesioned macaque, marmoset, and squirrel monkey in which the effects of experimental drugs on dyskinesia, parkinsonism, and psychosis was assessed. By comparing the results obtained at the preclinical level with those obtained in clinical settings, we have calculated the predictive value of each primate species for these disease manifestations/treatment-related complications.

There are limitations to our analysis that must be mentioned. First, as mentioned in the *Introduction*, the results of several studies, both preclinical and clinical, have not been published; and, although we aimed for exhaustiveness, our review is necessarily incomplete, which may have affected the

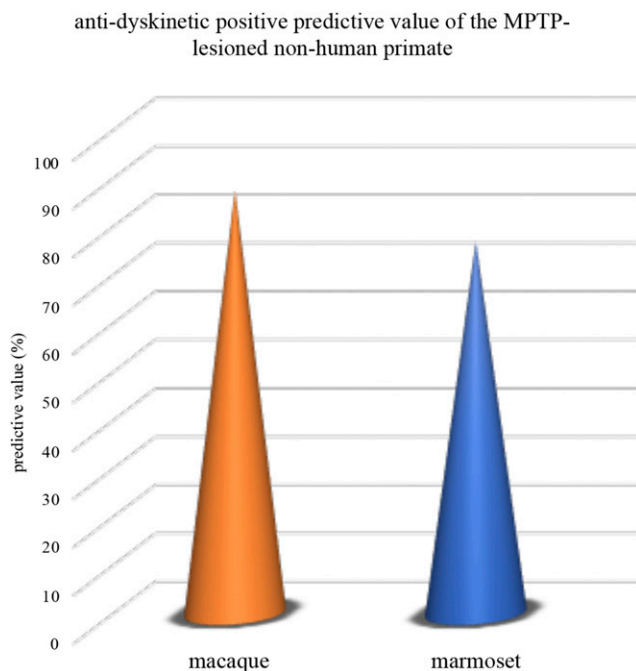


Fig. 3. The antidyskinetic positive predictive value of the MPTP-lesioned macaque is 87.5% and 76.9% for the MPTP-lesioned marmoset.

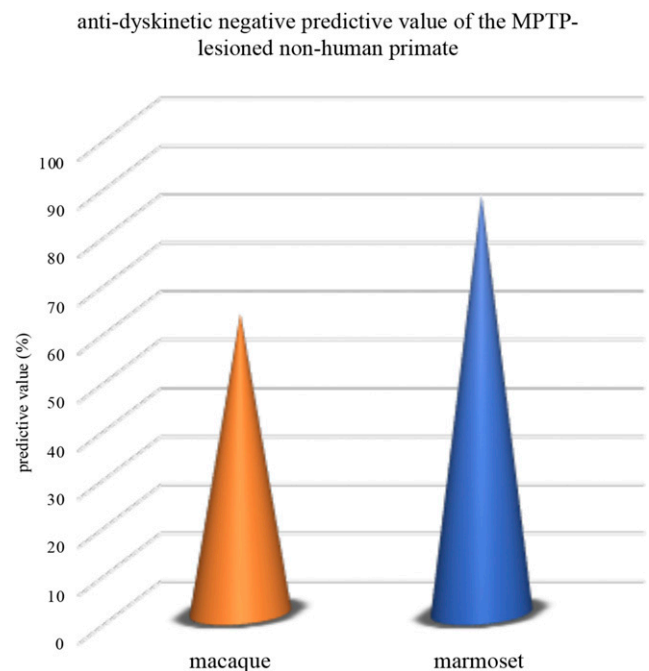


Fig. 4. The antidyskinetic negative predictive value of the MPTP-lesioned macaque is 61.9% and 86.4% for the MPTP-lesioned marmoset.

anti-dyskinetic false positive rate of the MPTP-lesioned non-human primate

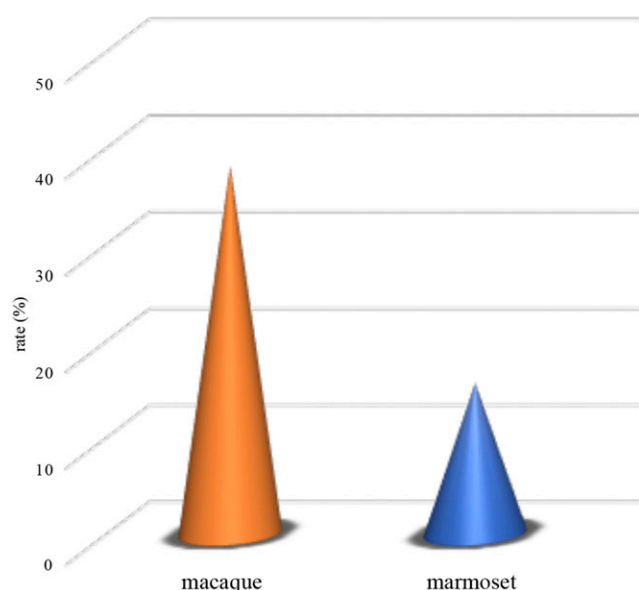


Fig. 5. The antidyskinetic false-positive rate of the MPTP-lesioned macaque is 38.1% and 15.6% for the MPTP-lesioned marmoset.

anti-parkinsonian negative predictive value of the MPTP-lesioned non-human primate

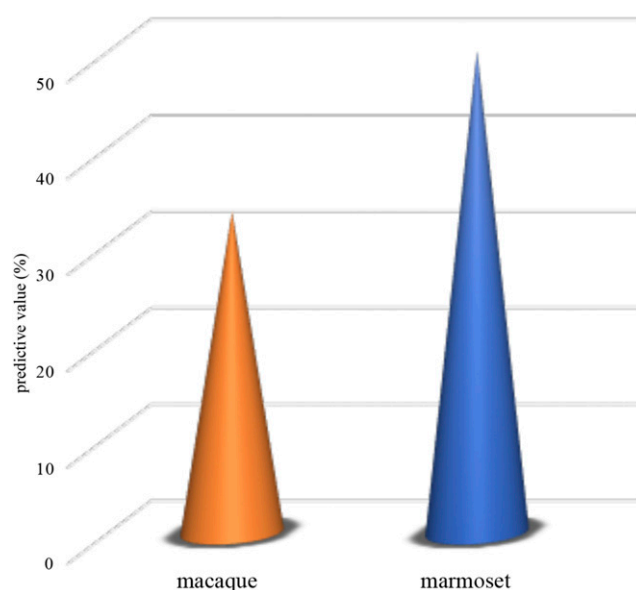


Fig. 7. The antiparkinsonian negative predictive value of the MPTP-lesioned macaque is 33.3% and 50.0% for the MPTP-lesioned marmoset.

various rates presented. Second, the methods of the clinical trials cited is highly variable, ranging from observational reports to randomized controlled trials; they were weighed equally here. Third, the method used in preclinical studies is, at times, different from the one used in clinical settings; one example is when a low dose of L-DOPA is administered to primates in combination with an agent with potential anti-parkinsonian effect as adjunct therapy. Lowering the L-DOPA

dose administered may be poorly tolerated by patients, which is why this approach is seldom used in clinical trials. Fourth, some clinical trials were performed in early stage PD patients, whereas the degree of parkinsonism after MPTP administration is severe and would correspond to advanced-stage PD. Finally, as several types of trials are part of our review, in some, PD patients were taking antiparkinsonian medication, in addition to L-DOPA, which is generally not the case in

anti-parkinsonian positive predictive value of the MPTP-lesioned non-human primate

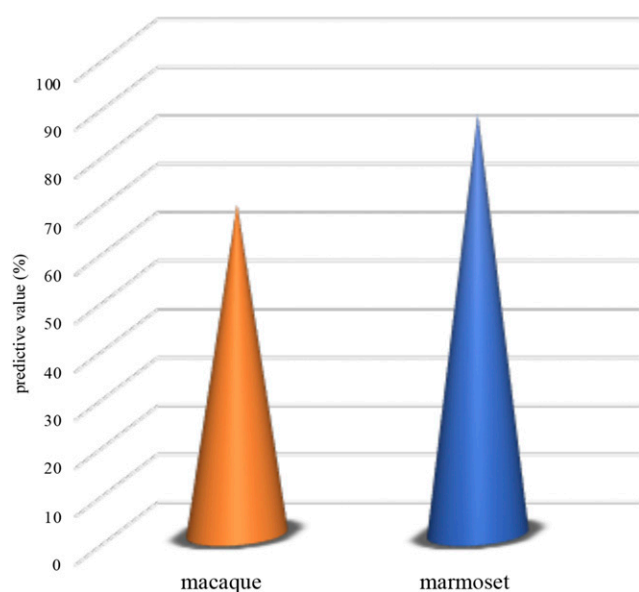


Fig. 6. The antiparkinsonian positive predictive value of the MPTP-lesioned macaque is 68.2% and 86.9% for the MPTP-lesioned marmoset.

anti-parkinsonian false positive rate of the MPTP-lesioned non-human primate

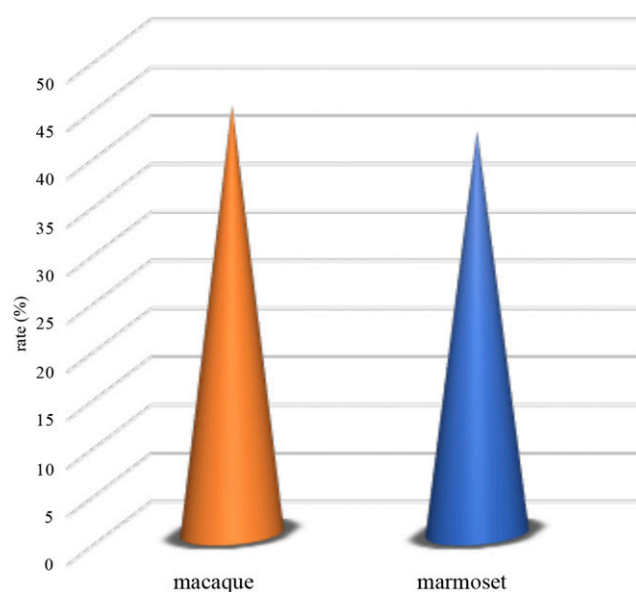


Fig. 8. The antiparkinsonian false-positive rate of the MPTP-lesioned macaque is 44.4% and 41.7% for the MPTP-lesioned marmoset.

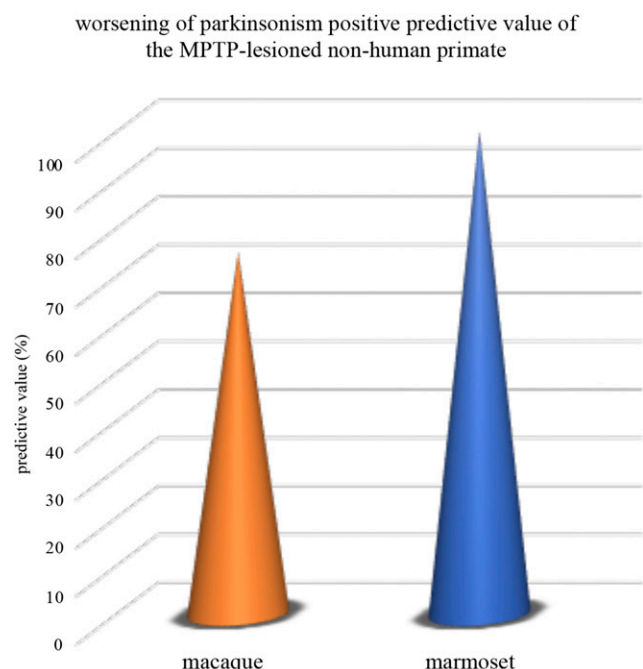


Fig. 9. The worsening of parkinsonism positive predictive value of the MPTP-lesioned macaque is 75.0% and 100.0% for the MPTP-lesioned marmoset.

primate studies, and the extent to which these molecules affected the results is undetermined.

Keeping these limitations in mind, the following general conclusions can be drawn:

- Relative to the antidyskinetic effect of drugs, the macaque has higher positive predictive value than the marmoset, but the marmoset has fewer false-positive results than the macaque. Both the macaque and the marmoset appear limited when it comes to predicting a detrimental effect of experimental drugs on dyskinesia.
- Relative to the antiparkinsonian action of drugs, the marmoset has a greater positive predictive value and fewer false-positive results than the macaque; both species have high predictive values when it comes to forecasting a potentially deleterious effect of drugs on parkinsonism.
- Relatively to the antipsychotic effect of drugs, comments can be made only for the marmoset, which has high positive predictive value.
- Compared with the macaque and the marmoset, the squirrel monkey has been used in a small number of studies, and few pharmacologic targets have been assessed in this primate species, which makes it impossible to calculate its predictive value.

At a time when the discovery and development process for drugs acting at the central nervous system level are facing challenges and have been marred by failures of high-profile candidates, it is our hope that this review will help in the planning and design of preclinical experiments aimed at testing the effects of drugs on L-DOPA-induced dyskinesia, parkinsonian disability, and dopaminergic psychosis by helping experimenters and sponsors plan their experiments in the animal model of PD with the highest translational potential for their specific endpoint.

Authorship Contributions

Participated in research design: Veyres, Huot.

Performed data analysis: Veyres, Huot.

Wrote or contributed to the writing of the manuscript: Veyres, Hamadjida, Huot.

References

- Gad SC, editor (2009) *Clinical Trials Handbook* [Internet]. Wiley, Hoboken.
- Agid Y, Pollak P, Bonnet AM, Signoret JL, and Lhermitte F (1979) Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson's disease. *Lancet* 1:570–572.
- Ahlskog JE, Wright KF, Muenter MD, and Adler CH (1996) Adjunctive cabergoline therapy of Parkinson's disease: comparison with placebo and assessment of dose responses and duration of effect. *Clin Neuropharmacol* 19:202–212.
- Akai T, Ozawa M, Yamaguchi M, Mizuta E, and Kuno S (1995) Behavioral involvement of central dopamine D1 and D2 receptors in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned parkinsonian cynomolgus monkeys. *Jpn J Pharmacol* 67:117–124.
- Antonini A, Tesi S, Zecchinelli A, Barone P, De Gaspari D, Canesi M, Sacilotto G, Meucci N, Mariani C, and Pezzoli G (2006) Randomized study of sertraline and low-dose amitriptyline in patients with Parkinson's disease and depression: effect on quality of life. *Mov Disord* 21:1119–1122.
- Baron MS and Dalton WB (2003) Quetiapine as treatment for dopaminergic-induced dyskinesias in Parkinson's disease. *Mov Disord* 18:1208–1209.
- Barone P, Lamb J, Ellis A, and Clarke Z (2007) Sumanitrol versus placebo or ropinirole for the adjunctive treatment of patients with advanced Parkinson's disease. *Mov Disord* 22:483–489.
- Bedard P, Parkes JD, and Marsden CD (1977) Nomifensine in Parkinson's disease. *Br J Clin Pharmacol* (4 Suppl) 2:187S–190S.
- Bedard PJ and Boucher R (1989) Effect of D1 receptor stimulation in normal and MPTP monkeys. *Neurosci Lett* 104:223–228.
- Bédard PJ, Di Paolo T, Falardeau P, and Boucher R (1986) Chronic treatment with L-DOPA, but not bromocriptine induces dyskinesia in MPTP-parkinsonian monkeys. Correlation with [3H]spiperone binding. *Brain Res* 379:294–299.
- Bélanger N, Grégoire L, Bédard P, and Di Paolo T (2003a) Estradiol and dehydroepiandrosterone potentiate levodopa-induced locomotor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys. *Endocrine* 21:97–101.
- Bélanger N, Grégoire L, Bédard PJ, and Di Paolo T (2006) DHEA improves symptomatic treatment of moderately and severely impaired MPTP monkeys. *Neurobiol Aging* 27:1684–1693.
- Bélanger N, Grégoire L, Hadj Tahar A, and Bédard PJ (2003b) Chronic treatment with small doses of cabergoline prevents dopa-induced dyskinesias in parkinsonian monkeys. *Mov Disord* 18:1436–1441.
- Belluzzi JD, Domino EF, May JM, Bankiewicz KS, and McAfee DA (1994) N-0923, a selective dopamine D2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease. *Mov Disord* 9:147–154.
- Berg D, Becker G, and Reiners K (1999) Reduction of dyskinesia and induction of akinesia induced by morphine in two parkinsonian patients with severe sciatica. *J Neural Transm (Vienna)* 106:725–728.
- Bespalov A, Steckler T, Altevogt B, Koustova E, Skolnick P, Deaver D, Millan MJ, Bastlund JF, Doller D, Witkin J, et al. (2016) Failed trials for central nervous system disorders do not necessarily invalidate preclinical models and drug targets. *Nat Rev Drug Discov* 15:516.
- Bezard E, Brefel C, Tison F, Peyro-Saint-Paul H, Ladure P, Rascol O, and Gross CE (1999) Effect of the alpha 2 adrenoceptor antagonist, idazoxan, on motor disabilities in MPTP-treated monkey. *Prog Neuropsychopharmacol Biol Psychiatry* 23:1237–1246.
- Bezard E, Ferry S, Mach U, Stark H, Leriche L, Boraud T, Gross C, and Sokoloff P (2003) Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. *Nat Med* 9:762–767.
- Bezard E, Hill MP, Crossman AR, Brothie JM, Michel A, Grimée R, and Klitgaard H (2004) Levodopa improves choreic levodopa-induced dyskinesia in the MPTP-treated macaque. *Eur J Pharmacol* 485:159–164.
- Bezard E, Muñoz A, Tronci E, Pioli EY, Li Q, Porras G, Björklund A, and Carta M (2013a) Anti-dyskinetic effect of amptiridine in animal models of L-DOPA-induced dyskinesia. *Neurosci Res* 77:242–246.
- Bezard E, Pioli EY, Li Q, Girard F, Mutel V, Keywood C, Tison F, Rascol O, and Poli SM (2014) The mGluR5 negative allosteric modulator dipraglurant reduces dyskinesia in the MPTP macaque model. *Mov Disord* 29:1074–1079.
- Bezard E, Tronci E, Pioli EY, Li Q, Porras G, Björklund A, and Carta M (2013b) Study of the antidyskinetic effect of eltopazine in animal models of levodopa-induced dyskinesia. *Mov Disord* 28:1088–1096.
- Bibbiani F, Costantini LC, Patel R, and Chase TN (2005a) Continuous dopaminergic stimulation reduces risk of motor complications in parkinsonian primates. *Exp Neurol* 192:73–78.
- Bibbiani F, Oh JD, and Chase TN (2001) Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models. *Neurology* 57:1829–1834.
- Bibbiani F, Oh JD, Kielaitis A, Collins MA, Smith C, and Chase TN (2005b) Combined blockade of AMPA and NMDA glutamate receptors reduces levodopa-induced motor complications in animal models of PD. *Exp Neurol* 196:422–429.
- Bibbiani F, Oh JD, Petzer JP, Castagnoli N, Jr, Chen JF, Schwarzschild MA, and Chase TN (2003) A2A antagonist prevents dopamine agonist-induced motor complications in animal models of Parkinson's disease. *Exp Neurol* 184:285–294.
- Blanchet P, Bédard PJ, Britton DR, and Kebejian JW (1993) Differential effect of selective D-1 and D-2 dopamine receptor agonists on levodopa-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-exposed monkeys. *J Pharmacol Exp Ther* 267:275–279.

- Blanchet PJ, Boucher R, and Bédard PJ (1994) Excitotoxic lateral pallidotomy does not relieve L-dopa-induced dyskinesia in MPTP parkinsonian monkeys. *Brain Res* **650**:32–39.
- Blanchet PJ, Calon F, Martel JC, Bédard PJ, Di Paolo T, Walters RR, and Piercey MF (1995) Continuous administration decreases and pulsatile administration increases behavioral sensitivity to a novel dopamine D2 agonist (U-91356A) in MPTP-exposed monkeys. *J Pharmacol Exp Ther* **272**:854–859.
- Blanchet PJ, Grondin R, and Bédard PJ (1996a) Dyskinesia and wearing-off following dopamine D1 agonist treatment in drug-naïve 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates. *Mov Disord* **11**:91–94.
- Blanchet PJ, Grondin R, Bédard PJ, Shiosaki K, and Britton DR (1996b) Dopamine D1 receptor desensitization profile in MPTP-lesioned primates. *Eur J Pharmacol* **309**:13–20.
- Blanchet PJ, Konitsiotis S, and Chase TN (1997) Motor response to a dopamine D3 receptor preferring agonist compared to apomorphine in levodopa-primed 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys. *J Pharmacol Exp Ther* **283**:794–799.
- Blanchet PJ, Konitsiotis S, and Chase TN (1998) Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Mov Disord* **13**:798–802.
- Blanchet PJ, Konitsiotis S, Whittemore ER, Zhou ZL, Woodward RM, and Chase TN (1999) Differing effects of N-methyl-D-aspartate receptor subtype selective antagonists on dyskinesias in levodopa-treated 1-methyl-4-phenyl-tetrahydropyridine monkeys. *J Pharmacol Exp Ther* **290**:1034–1040.
- Boman K and Meurman T (1970) Investigations on the effect of some drugs on the Parkinsonian rigidity. *Acta Neurol Scand* **46**:71–84.
- Borghain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, et al.; Study 016 Investigators (2014a) Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord* **29**:229–237.
- Borghain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, et al.; Study 018 Investigators (2014b) Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* **29**:1273–1280.
- Braun A, Fabbri G, Mouradian MM, Serrati C, Barone P, and Chase TN (1987) Selective D-1 dopamine receptor agonist treatment of Parkinson's disease. *J Neural Transm (Vienna)* **68**:41–50.
- Bronzova J, Sampaio C, Hauser RA, Lang AE, Rascol O, Theeuwes A, van de Witte SV, and van Scharrenburg G; Bruegel Study Group (2010) Double-blind study of pramipexole, a new partial dopamine agonist, in early Parkinson's disease. *Mov Disord* **25**:738–746.
- Burns RS, Chuiue CC, Markey SP, Ebert MH, Jacobowitz DM, and Kopin IJ (1983) A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc Natl Acad Sci USA* **80**:4546–4550.
- Butzer JF, Silver DE, and Sahs AL (1975) Amantadine in Parkinson's disease. A double-blind, placebo-controlled, crossover study with long-term follow-up. *Neurology* **25**:603–606.
- Calon F, Goulet M, Blanchet PJ, Martel JC, Piercey MF, Bédard PJ, and Di Paolo T (1995) Levodopa or D2 agonist induced dyskinesia in MPTP monkeys: correlation with changes in dopamine and GABA receptors in the striatopallidal complex. *Brain Res* **680**:43–52.
- Calon F, Morissette M, Ghribi O, Goulet M, Grondin R, Blanchet PJ, Bédard PJ, and Di Paolo T (2002) Alteration of glutamate receptors in the striatum of dyskinesia 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys following dopamine agonist treatment. *Prog Neuropsychopharmacol Biol Psychiatry* **26**:127–138.
- Calon F, Morissette M, Goulet M, Grondin R, Blanchet PJ, Bédard PJ, and Di Paolo T (1999) Chronic D1 and D2 dopaminomimetic treatment of MPTP-denervated monkeys: effects on basal ganglia GABA(A)/benzodiazepine receptor complex and GABA content. *Neurochem Int* **35**:81–91.
- Calon F, Morissette M, Goulet M, Grondin R, Blanchet PJ, Bédard PJ, and Di Paolo T (2000) 125I-CGP 64213 binding to GABA(B) receptors in the brain of monkeys: effect of MPTP and dopaminomimetic treatments. *Exp Neurol* **163**:191–199.
- Cao X, Liang L, Hadcock JR, Iredale PA, Griffith DA, Menniti FS, Factor S, Greenamyre JT, and Papa SM (2007) Blockade of cannabinoid type 1 receptors augments the antiparkinsonian action of levodopa without affecting dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated rhesus monkeys. *J Pharmacol Exp Ther* **323**:318–326.
- Carpentier AF, Bonnet AM, Vidailhet M, and Agid Y (1996) Improvement of levodopa-induced dyskinesia by propranolol in Parkinson's disease. *Neurology* **46**:1548–1551.
- Castro-Caldas A, Delwaide P, Jost W, Merello M, Williams A, Lamberti P, Aguilar M, Del Signore S, and Cesaro P; Parkinson-Control Study Group (2006) The Parkinson-control study: a 1-year randomized, double-blind trial comparing piribedil (150 mg/day) with bromocriptine (25 mg/day) in early combination with levodopa in Parkinson's disease. *Mov Disord* **21**:500–509.
- Cattaneo C, Ferla RL, Bonizzoni E, and Sardino M (2015) Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's disease: a post-hoc analysis. *J Parkinsons Dis* **5**:475–481.
- Close SP, Elliott PJ, Hayes AG, and Marriott AS (1990) Effects of classical and novel agents in a MPTP-induced reversible model of Parkinson's disease. *Psychopharmacology (Berl)* **102**:295–300.
- Clough CG, Bergmann KJ, and Yahr MD (1984) Cholinergic and dopaminergic mechanisms in Parkinson's disease after long-term L-DOPA administration. *Adv Neurol* **40**:131–140.
- Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, and Pangalos MN (2014) Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nat Rev Drug Discov* **13**:419–431.
- Coppen A, Metcalfe M, Carroll JD, and Morris JG (1972) Levodopa and L-tryptophan therapy in Parkinsonism. *Lancet* **1**:654–658.
- Corsini GU, Del Zompo M, Gessa GL, and Mangoni A (1979) Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. *Lancet* **1**:954–956.
- Cox H, Togasaki DM, Chen L, Langston JW, Di Monte DA, and Quik M (2007) The selective kappa-opioid receptor agonist U50,488 reduces L-dopa-induced dyskinesias but worsens parkinsonism in MPTP-treated primates. *Exp Neurol* **205**:101–107.
- Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, and Ballard C (2014) Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet* **383**:533–540.
- Davis GC, Williams AC, Markey SP, Ebert MH, Caine ED, Reichert CM, and Kopin IJ (1979) Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res* **1**:249–254.
- Del Dotto P, Pavese N, Gambaccini G, Bernardini S, Metman LV, Chase TN, and Bonuccelli U (2001) Intravenous amantadine improves levodopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov Disord* **16**:515–520.
- Deuschl G, Vaitkus A, Fox GC, Roscher T, Schremmer D, and Gordin A; CAMP Study Group (2007) Efficacy and tolerability of entacapone versus cabergoline in parkinsonian patients suffering from wearing-off. *Mov Disord* **22**:1550–1555.
- Di Paolo T, Bédard P, Daigle M, and Boucher R (1986) Long-term effects of MPTP on central and peripheral catecholamine and indoleamine concentrations in monkeys. *Brain Res* **379**:286–293.
- Di Paolo T, Grégoire L, Feuerbach D, Elbast W, Weiss M, and Gomez-Mancilla B (2014) AQW051, a novel and selective nicotinic acetylcholine receptor $\alpha 7$ partial agonist, reduces L-Dopa-induced dyskinesias and extends the duration of L-Dopa effects in parkinsonian monkeys. *Parkinsonism Relat Disord* **20**:1119–1123.
- Doan VD, Grondin R, Hadj Tahar A, Grégoire L, and Bédard PJ (1999) Effect of the selective D1 antagonists SCH 23390 and NNC 01-0112 on the delay, duration, and improvement of behavioral responses to dopaminergic agents in MPTP-treated monkeys. *Clin Neuropharmacol* **22**:281–287.
- Domino EF and Ni L (1998a) Trihexyphenidyl interactions with the dopamine D1-selective receptor agonist SKF-82958 and the D2-selective receptor agonist N-0923 in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced hemiparkinsonian monkeys. *J Pharmacol Exp Ther* **284**:307–311.
- Domino EF and Ni L (1998b) Trihexyphenidyl potentiation of L-DOPA: reduced effectiveness three years later in MPTP-induced chronic hemiparkinsonian monkeys. *Exp Neurol* **152**:238–242.
- Doshay LJ (1956) Five-year study of benztropine (cogentin) methanesulfonate; outcome in three hundred two cases of paralysis agitans. *J Am Med Assoc* **162**:1031–1034.
- Durif F, Debilly B, Galitzky M, Morand D, Viallet F, Borg M, Thobois S, Broussolle E, and Rascol O (2004) Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* **62**:381–388.
- Durif F, Vidailhet M, Assal F, Roche C, Bonnet AM, and Agid Y (1997) Low-dose clozapine improves dyskinesias in Parkinson's disease. *Neurology* **48**:658–662.
- Duvoisin RC (1967) Cholinergic-anticholinergic antagonism in parkinsonism. *Arch Neurol* **17**:124–136.
- Ekesbo A, Andrén PE, Gunne LM, and Tedroff J (1997) (-)-OSU 6162 inhibits levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Neuroreport* **8**:2567–2570.
- Emre M, Rinne UK, Rascol A, Lees A, Agid Y, and Lataste X (1992) Effects of a selective partial D1 agonist, CY 208-243, in de novo patients with Parkinson disease. *Mov Disord* **7**:239–243.
- Factor SA, Wolski K, Togasaki DM, Huyck S, Cantillon M, Ho TW, Hauser RA, and Pourcher E (2013) Long-term safety and efficacy of pramipexole in subjects with fluctuating Parkinson's disease. *Mov Disord* **28**:817–820.
- Falardeau P, Bouchard S, Bédard PJ, Boucher R, and Di Paolo T (1988) Behavioral and biochemical effect of chronic treatment with D-1 and/or D-2 dopamine agonists in MPTP monkeys. *Eur J Pharmacol* **150**:59–66.
- Fénelon G, Giménez-Roldán S, Montastruc JL, Bermejo F, Durif F, Bourdeix I, Péré JJ, Galiano L, and Schadrack J (2003) Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations. A randomized, double-blind, multicentre study. *J Neural Transm (Vienna)* **110**:239–251.
- Fernandez HH, Friedman JH, Jacques C, and Rosenfeld M (1999) Quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord* **14**:484–487.
- Fernandez HH, Trieschmann ME, Burke MA, Jacques C, and Friedman JH (2003) Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. *Mov Disord* **18**:510–514.
- Fidalgo C, Ko WK, Tronci E, Li Q, Stancampiano R, Chuan Q, Bezard E, and Carta M (2015) Effect of serotonin transporter blockade on L-DOPA-induced dyskinesia in animal models of Parkinson's disease. *Neuroscience* **298**:389–396.
- Filion M, Tremblay L, and Bédard PJ (1991) Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* **547**:152–161.
- Filipová M, Filip V, Macek Z, Müllerová S, Marková J, Kás S, Zizková B, Krivka J, Votavová A, and Krejčová H (1988) Terguride in parkinsonism: a multicenter trial. *Eur Arch Psychiatry Neurol Sci* **237**:298–303.
- Fox S, Silverdale M, Kellett M, Davies R, Steiger M, Fletcher N, Crossman A, and Brothie J (2004) Non-subtype-selective opioid receptor antagonism in treatment of levodopa-induced motor complications in Parkinson's disease. *Mov Disord* **19**:554–560.
- Fox SH, Henry B, Hill M, Crossman A, and Brothie J (2002) Stimulation of cannabinoid receptors reduces levodopa-induced dyskinesia in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* **17**:1180–1187.
- Fox SH, Henry B, Hill MP, Peggs D, Crossman AR, and Brothie JM (2001) Neural mechanisms underlying peak-dose dyskinesia induced by levodopa and apomorphine are distinct: evidence from the effects of the $\alpha(2)$ adrenoceptor antagonist idazoxan. *Mov Disord* **16**:642–650.

- Fox SH, Lang AE, and Brotchie JM (2006a) Translation of nondopaminergic treatments for levodopa-induced dyskinesia from MPTP-lesioned nonhuman primates to phase IIa clinical studies: keys to success and roads to failure. *Mov Disord* **21**: 1578–1594.
- Fox SH, Visanji NP, Johnston TH, Gomez-Ramirez J, Voon V, and Brotchie JM (2006b) Dopamine receptor agonists and levodopa and inducing psychosis-like behavior in the MPTP primate model of Parkinson disease. *Arch Neurol* **63**: 1343–1344.
- Frackiewicz EJ, Jhee SS, Shiovitz TM, Webster J, Topham C, Dockens RC, Whigan D, Salazar DE, and Cutler NR (2002) Brasofensine treatment for Parkinson's disease in combination with levodopa/carbidopa. *Ann Pharmacother* **36**:225–230.
- The French Clozapine Parkinson Study Group (1999) Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet* **353**:2041–2042.
- Gagnon C, Bédard PJ, and Di Paolo T (1990) Effect of chronic treatment of MPTP monkeys with dopamine D-1 and/or D-2 receptor agonists. *Eur J Pharmacol* **178**: 115–120.
- Gagnon C, Gomez-Mancilla B, Bédard PJ, and Di Paolo T (1993) Chronic CY 208-243 treatment of MPTP-monkeys causes regional changes of dopamine and GABA receptors. *Neurosci Lett* **163**:31–35.
- Gagnon C, Gomez-Mancilla B, Markstein R, Bédard PJ, and Di Paolo T (1995) Effect of adding the D-1 agonist CY 208-243 to chronic bromocriptine treatment of MPTP-monkeys: regional changes of brain dopamine receptors. *Prog Neuropsychopharmacol Biol Psychiatry* **19**:667–676.
- Galvan A, Devergnas A, Pittard D, Masilamoni G, Vuong J, Daniels JS, Morrison RD, Lindsley CW, and Wichmann T (2016) Lack of antiparkinsonian effects of systemic injections of the specific T-type calcium channel blocker ML218 in MPTP-treated monkeys. *ACS Chem Neurosci* **7**:1543–1551.
- Gerstenbrand F, Binder H, Kozma C, Pusch ST, and Reisner Th (1975) Infusion therapy with mif (melanocyte inhibiting factor) in Parkinson's disease (author's transl). *Wien Klin Wochenschr* **87**:822–823.
- Giladi N, Borojerd B, Korczyn AD, Burn DJ, Clarke CE, and Schapira AH; SP513 investigators (2007) Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. *Mov Disord* **22**:2398–2404.
- Gnanalingham KK, Erol DD, Hunter AJ, Smith LA, Jenner P, and Marsden CD (1995a) Differential anti-parkinsonian effects of benzazepine D1 dopamine agonists with varying efficacies in the MPTP-treated common marmoset. *Psychopharmacology (Berl)* **117**:275–286.
- Gnanalingham KK, Hunter AJ, Jenner P, and Marsden CD (1995b) The differential behavioural effects of benzazepine D1 dopamine agonists with varying efficacies, co-administered with quinpirole in primate and rodent models of Parkinson's disease. *Psychopharmacology (Berl)* **117**:287–297.
- Gnanalingham KK, Hunter AJ, Jenner P, and Marsden CD (1995c) Selective dopamine antagonist pretreatment on the antiparkinsonian effects of benzazepine D1 dopamine agonists in rodent and primate models of Parkinson's disease—the differential effects of D1 dopamine antagonists in the primate. *Psychopharmacology (Berl)* **117**:403–412.
- Goetz CG, Damier P, Hickey C, Laska E, Müller T, Olanow CW, Rascol O, and Russ H (2007) Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial. *Mov Disord* **22**:179–186.
- Goetz CG, Laska E, Hickey C, Damier P, Müller T, Nutt J, Warren Olanow C, Rascol O, and Russ H (2008) Placebo influences on dyskinesia in Parkinson's disease. *Mov Disord* **23**:700–707.
- Goetz CG, Stebbins GT, Chung KA, Nicholas AP, Hauser RA, Merkitich D, and Stacy MA (2017) Topiramate as an adjunct to amantadine in the treatment of dyskinesia in parkinson's disease: a randomized, double-blind, placebo-controlled multicenter study. *Mov Disord* **32**:1335–1336.
- Goetz CG, Tanner CM, and Klawans HL (1984) Bupropion in Parkinson's disease. *Neurology* **34**:1092–1094.
- Gomez-Mancilla B and Bédard PJ (1991) Effect of D1 and D2 agonists and antagonists on dyskinesia produced by L-dopa in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys. *J Pharmacol Exp Ther* **259**:409–413.
- Gomez-Mancilla B and Bédard PJ (1992a) Effect of chronic treatment with (+)-PHNO, a D2 agonist in MPTP-treated monkeys. *Exp Neurol* **117**:185–188.
- Gomez-Mancilla B and Bédard PJ (1992b) Effect of estrogen and progesterone on L-dopa induced dyskinesia in MPTP-treated monkeys. *Neurosci Lett* **135**:129–132.
- Gomez-Mancilla B and Bédard PJ (1993) Effect of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. *Clin Neuropharmacol* **16**:418–427.
- Gomez-Mancilla B, Boucher R, and Bédard PJ (1991) Effect of clonidine and atropine on rest tremor in the MPTP monkey model of parkinsonism. *Clin Neuropharmacol* **14**:359–366.
- Gomez-Mancilla B, Boucher R, and Bédard PJ (1992a) Effect of LY 171555 and CY 208-243 on tremor suppression in the MPTP monkey model of parkinsonism. *Mov Disord* **7**:43–47.
- Gomez-Mancilla B, Boucher R, Gagnon C, Di Paolo T, Markstein R, and Bédard PJ (1993) Effect of adding the D1 agonist CY 208-243 to chronic bromocriptine treatment. I: evaluation of motor parameters in relation to striatal catecholamine content and dopamine receptors. *Mov Disord* **8**:144–150.
- Gomez-Mancilla B, Latulippe JF, Boucher R, and Bédard PJ (1992b) Effect of ethosuximide on rest tremor in the MPTP monkey model. *Mov Disord* **7**:137–141.
- Gomez-Ramirez J, Johnston TH, Visanji NP, Fox SH, and Brotchie JM (2006) Histamine H3 receptor agonists reduce L-dopa-induced chorea, but not dystonia, in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* **21**:839–846.
- Gordon PH, Pullman SL, Louis ED, Frucht SJ, and Fahn S (2002) Mirtazapine in Parkinsonian tremor. *Parkinsonism Relat Disord* **9**:125–126.
- Goulet M, Grondin R, Blanchet PJ, Bédard PJ, and Di Paolo T (1996) Dyskinesias and tolerance induced by chronic treatment with a D1 agonist administered in pulsatile or continuous mode do not correlate with changes of putaminal D1 receptors in drug-naïve MPTP monkeys. *Brain Res* **719**:129–137.
- Goulet M, Grondin R, Morissette M, Maltais S, Falardeau P, Bédard PJ, and Di Paolo T (2000) Regulation by chronic treatment with cabergoline of dopamine D1 and D2 receptor levels and their expression in the striatum of Parkinsonian-monkeys. *Prog Neuropsychopharmacol Biol Psychiatry* **24**:607–617.
- Goulet M, Morissette M, Calon F, Blanchet PJ, Falardeau P, Bédard PJ, and Di Paolo T (1997) Continuous or pulsatile chronic D2 dopamine receptor agonist (U91566A) treatment of drug-naïve 4-phenyl-1,2,3,6-tetrahydropyridine monkeys differentially regulates brain D1 and D2 receptor expression: in situ hybridization histochemical analysis. *Neuroscience* **79**:497–507.
- Goulet M, Morissette M, Grondin R, Falardeau P, Bédard PJ, Rostène W, and Di Paolo T (1999) Neurotensin receptors and dopamine transporters: effects of MPTP lesioning and chronic dopaminergic treatments in monkeys. *Synapse* **32**: 153–164.
- Grandas F, Quinn N, Critchley P, Rohan A, Marsden CD, and Stahl SM (1987) Antiparkinsonian activity of a single oral dose of PHNO. *Mov Disord* **2**:47–51.
- Greenamyre JT, Eller RV, Zhang Z, Ovadia A, Kurlan R, and Gash DM (1994) Antiparkinsonian effects of remacemide hydrochloride, a glutamate antagonist, in rodent and primate models of Parkinson's disease. *Ann Neurol* **35**:655–661.
- Grégoire L, Jourdain VA, Townsend M, Roach A, and Di Paolo T (2013) Safinamide reduces dyskinesias and prolongs L-DOPA antiparkinsonian effect in parkinsonian monkeys. *Parkinsonism Relat Disord* **19**:508–514.
- Grégoire L, Morin N, Ouattara B, Gasparini F, Bilbe G, Johns D, Vranesic I, Sahasranaman S, Gomez-Mancilla B, and Di Paolo T (2011) The acute antiparkinsonian and antidyskinetic effect of AFQ056, a novel metabotropic glutamate receptor type 5 antagonist, in L-Dopa-treated parkinsonian monkeys. *Parkinsonism Relat Disord* **17**:270–276.
- Grégoire L, Rassoulpour A, Guidetti P, Samadi P, Bédard PJ, Izzo E, Schwarcz R, and Di Paolo T (2008) Prolonged kynurenine 3-hydroxylase inhibition reduces development of levodopa-induced dyskinesias in parkinsonian monkeys. *Behav Brain Res* **186**:161–167.
- Grégoire L, Samadi P, Graham J, Bédard PJ, Bartoszyk GD, and Di Paolo T (2009) Low doses of sarizotan reduce dyskinesias and maintain antiparkinsonian efficacy of L-Dopa in parkinsonian monkeys. *Parkinsonism Relat Disord* **15**:445–452.
- Grégoire L, Smith T, Senanayake V, Mochizuki A, Miville-Godbout E, Goodenow D, and Di Paolo T (2015) Plasmalogen precursor analog treatment reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Behav Brain Res* **286**:328–337.
- Grondin R, Bédard PJ, Britton DR, and Shiosaki K (1997) Potential therapeutic use of the selective dopamine D1 receptor agonist, A-86929: an acute study in parkinsonian levodopa-primed monkeys. *Neurology* **49**:421–426.
- Grondin R, Bédard PJ, Hadj Tahar A, Grégoire L, Mori A, and Kase H (1999a) Antiparkinsonian effect of a new selective adenosine A2A receptor antagonist in MPTP-treated monkeys. *Neurology* **52**:1673–1677.
- Grondin R, Doan VD, Grégoire L, and Bédard PJ (1999b) D1 receptor blockade improves L-dopa-induced dyskinesia but worsens parkinsonism in MPTP monkeys. *Neurology* **52**:771–776.
- Grondin R, Goulet M, Di Paolo T, and Bédard PJ (1996) Cabergoline, a long-acting dopamine D2-like receptor agonist, produces a sustained antiparkinsonian effect with transient dyskinesias in parkinsonian drug-naïve primates. *Brain Res* **735**: 298–306.
- Grondin R, Goulet M, Morissette M, Bédard PJ, and Di Paolo T (1999c) Dopamine D1 receptor mRNA and receptor levels in the striatum of MPTP monkeys chronically treated with SKF-82958. *Eur J Pharmacol* **378**:259–263.
- Grondin R, Hadj Tahar A, Doan VD, Ladure P, and Bédard PJ (2000) Noradrenoceptor antagonism with idazoxan improves L-dopa-induced dyskinesias in MPTP monkeys. *Naunyn-Schmiedeberg Arch Pharmacol* **361**:181–186.
- Gruchet R (1952) Scopolamine in parkinsonism. *Therapie* **7**:114–121.
- Hadj Tahar A, Bélanger N, Bangassoro E, Grégoire L, and Bédard PJ (2000a) Antidyskinetic effect of JL-18, a clozapine analog, in parkinsonian monkeys. *Eur J Pharmacol* **399**:183–186.
- Hadj Tahar A, Ekesbo A, Grégoire L, Bangassoro E, Svensson KA, Tedroff J, and Bédard PJ (2001) Effects of acute and repeated treatment with a novel dopamine D2 receptor ligand on L-DOPA-induced dyskinesias in MPTP monkeys. *Eur J Pharmacol* **412**:247–254.
- Hadj Tahar A, Grégoire L, Bangassoro E, and Bédard PJ (2000b) Sustained cabergoline treatment reverses levodopa-induced dyskinesias in parkinsonian monkeys. *Clin Neuropharmacol* **23**:195–202.
- Hadj Tahar A, Grégoire L, Darré A, Bélanger N, Meltzer L, and Bédard PJ (2004) Effect of a selective glutamate antagonist on L-dopa-induced dyskinesias in drug-naïve parkinsonian monkeys. *Neurobiol Dis* **15**:171–176.
- Hamadja A, Nuara SG, Gourdon JC, and Huot P (2018) The effect of mianserin on the severity of psychosis and dyskinesia in the parkinsonian marmoset. *Prog Neuropsychopharmacol Biol Psychiatry* **81**:367–371.
- Hamadja A, Nuara SG, Veyres N, Frouni I, Kwan C, Sid-Otmane L, Harraka MJ, Gourdon JC, and Huot P (2017) The effect of mirtazapine on dopaminergic psychosis and dyskinesia in the parkinsonian marmoset. *Psychopharmacology (Berl)* **234**:905–911.
- Hansard MJ, Jackson MJ, Smith LA, Rose S, and Jenner P (2011) A major metabolite of bupropion reverses motor deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated common marmosets. *Behav Pharmacol* **22**:269–274.
- Hansard MJ, Smith LA, Jackson MJ, Cheetham SC, and Jenner P (2002a) Dopamine reuptake inhibition and failure to evoke dyskinesia in MPTP-treated primates. *Eur J Pharmacol* **451**:157–160.
- Hansard MJ, Smith LA, Jackson MJ, Cheetham SC, and Jenner P (2002b) Dopamine, but not norepinephrine or serotonin, reuptake inhibition reverses motor deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates. *J Pharmacol Exp Ther* **303**:952–958.
- Hansard MJ, Smith LA, Jackson MJ, Cheetham SC, and Jenner P (2004) The monoamine reuptake inhibitor BTS 74 398 fails to evoke established dyskinesia but does not synergise with levodopa in MPTP-treated primates. *Mov Disord* **19**: 15–21.

- Hauser RA, Cantillon M, Pourcher E, Micheli F, Mok V, Onofrij M, Huyck S, and Wolski K (2011) Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. *Lancet Neurol* **10**: 221–229.
- Hauser RA, Hubble JP, and Truong DD; Istradefylline US-001 Study Group (2003) Randomized trial of the adenosine A(2A) receptor antagonist istradefylline in advanced PD. *Neurology* **61**:297–303.
- Hauser RA, Shulman LM, Trugman JM, Roberts JW, Mori A, Ballerini R, and Sussman NM; Istradefylline 6002-US-013 Study Group (2008) Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Mov Disord* **23**:2177–2185.
- Hauser RA, Stocchi F, Rascol O, Huyck SB, Capece R, Ho TW, Sklar P, Lines C, Michelson D, and Hewitt D (2015) Preladenant as an adjunctive therapy with levodopa in Parkinson disease: two randomized clinical trials and lessons learned. *JAMA Neurol* **72**:1491–1500.
- Hauser RA and Zesiewicz TA (1997) Sertraline for the treatment of depression in Parkinson's disease. *Mov Disord* **12**:756–759.
- Hely MA, Morris JG, Reid WG, O'Sullivan DJ, Williamson PM, Rail D, Broe GA, and Margrie S (1994) The Sydney multicentre study of Parkinson's disease: a randomised, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. *J Neurol Neurosurg Psychiatry* **57**:903–910.
- Henry B, Fox SH, Crossman AR, and Brotchie JM (2001) Mu- and delta-opioid receptor antagonists reduce levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. *Exp Neurol* **171**:139–146.
- Henry B, Fox SH, Peggs D, Crossman AR, and Brotchie JM (1999) The alpha2-adrenergic receptor antagonist idazoxan reduces dyskinesia and enhances antiparkinsonian actions of L-dopa in the MPTP-lesioned primate model of Parkinson's disease. *Mov Disord* **14**:744–753.
- Hill MP, Bezard E, McGuire SG, Crossman AR, Brotchie JM, Michel A, Grimée R, and Klitgaard H (2003) Novel antiepileptic drug levetiracetam decreases dyskinesia elicited by L-dopa and ropinirole in the MPTP-lesioned marmoset. *Mov Disord* **18**:1301–1305.
- Hill MP, Brotchie JM, Crossman AR, Bezard E, Michel A, Grimée R, and Klitgaard H (2004a) Levetiracetam interferes with the L-dopa priming process in MPTP-lesioned drug-naïve marmosets. *Clin Neuropharmacol* **27**:171–177.
- Hill MP, Ravenscroft P, Bezard E, Crossman AR, Brotchie JM, Michel A, Grimée R, and Klitgaard H (2004b) Levetiracetam potentiates the antidyskinetic action of amantadine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model of Parkinson's disease. *J Pharmacol Exp Ther* **310**:386–394.
- Hill MP, Ravenscroft P, McGuire SG, Brotchie JM, Crossman AR, Rochat C, and Millan MJ (2006) Antiparkinsonian effects of the novel D3/D2 dopamine receptor agonist, S32504, in MPTP-lesioned marmosets: mediation by D2, not D3, dopamine receptors. *Mov Disord* **21**:2090–2095.
- Hille CJ, Fox SH, Maneuf YP, Crossman AR, and Brotchie JM (2001) Antiparkinsonian action of a delta opioid agonist in rodent and primate models of Parkinson's disease. *Exp Neurol* **172**:189–198.
- Hodgson RA, Bedard PJ, Varty GB, Kazdoba TM, Di Paolo T, Grzelak ME, Pond AJ, Hadjitarah A, Belanger N, Gregoire L, et al. (2010) Preladenant, a selective A(2A) receptor antagonist, is active in primate models of movement disorders. *Exp Neurol* **225**:384–390.
- Hsu A, Togasaki DM, Bezard E, Sokoloff P, Langston JW, Di Monte DA, and Quirk M (2004) Effect of the D3 dopamine receptor partial agonist BP897 [N-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide] on L-3,4-dihydroxyphenylalanine-induced dyskinesias and parkinsonism in squirrel monkeys. *J Pharmacol Exp Ther* **311**:770–777.
- Huot P, Johnston TH, Fox SH, and Brotchie JM (2015a) Pioglitazone may impair L-DOPA anti-parkinsonian efficacy in the MPTP-lesioned macaque: results of a pilot study. *Synapse* **69**:99–102.
- Huot P, Johnston TH, Fox SH, Newman-Tancredi A, and Brotchie JM (2015b) The highly-selective 5-HT(1A) agonist F15599 reduces L-DOPA-induced dyskinesia without compromising anti-parkinsonian benefits in the MPTP-lesioned macaque. *Neuropharmacology* **97**:306–311.
- Huot P, Johnston TH, Gandy MN, Reyes MG, Fox SH, Piggott MJ, and Brotchie JM (2012a) The monoamine re-uptake inhibitor UWA-101 improves motor fluctuations in the MPTP-lesioned common marmoset. *PLoS One* **7**:e45587.
- Huot P, Johnston TH, Koprich JB, Aman A, Fox SH, and Brotchie JM (2012b) 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* **342**:576–585.
- Huot P, Johnston TH, Lewis KD, Koprich JB, Reyes MG, Fox SH, Piggott MJ, and Brotchie JM (2011) Characterization of 3,4-methylenedioxymethamphetamine (MDMA) enantiomers in vitro and in the MPTP-lesioned primate: R-MDMA reduces severity of dyskinesia, whereas S-MDMA extends duration of ON-time. *J Neurosci* **31**:7190–7198.
- Huot P, Johnston TH, Lewis KD, Koprich JB, Reyes MG, Fox SH, Piggott MJ, and Brotchie JM (2014) UWA-121, a mixed dopamine and serotonin re-uptake inhibitor, enhances L-DOPA anti-parkinsonian action without worsening dyskinesia or psychosis-like behaviours in the MPTP-lesioned common marmoset. *Neuropharmacology* **82**:76–87.
- Huot P, Johnston TH, Snoeren T, Koprich JB, Hill MP, Fox SH, and Brotchie JM (2013) Use of catechol O-methyltransferase inhibition to minimize L-3,4-dihydroxyphenylalanine-induced dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque. *Eur J Neurosci* **37**:831–838.
- Huot P, Lévesque M, Morissette M, Calon F, Dridi M, Di Paolo T, and Parent A (2008) L-Dopa treatment abolishes the numerical increase in striatal dopaminergic neurons in parkinsonian monkeys. *J Chem Neuroanat* **35**:77–84.
- Hyacinthe C, Barraud Q, Tison F, Bezard E, and Ghorayeb I (2014) D1 receptor agonist improves sleep-wake parameters in experimental parkinsonism. *Neurobiol Dis* **63**:20–24.
- Ikeguchi K and Kuroda A (1995) Mianserin treatment of patients with psychosis induced by antiparkinsonian drugs. *Eur Arch Psychiatry Clin Neurosci* **244**: 320–324.
- Iravani MM, Jackson MJ, Kuoppamäki M, Smith LA, and Jenner P (2003) 3,4-methylenedioxymethamphetamine (ecstasy) inhibits dyskinesia expression and normalizes motor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates. *J Neurosci* **23**:9107–9115.
- Iravani MM, Tayarani-Binazir K, Chu WB, Jackson MJ, and Jenner P (2006) In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates, the selective 5-hydroxytryptamine 1a agonist (R)-(+)-8-OHDPAT inhibits levodopa-induced dyskinesia but only with increased motor disability. *J Pharmacol Exp Ther* **319**: 1225–1234.
- Jackson MJ, Al-Barghouthy G, Pearce RK, Smith L, Hagan JJ, and Jenner P (2004) Effect of 5-HT1B/D receptor agonist and antagonist administration on motor function in haloperidol and MPTP-treated common marmosets. *Pharmacol Biochem Behav* **79**:391–400.
- Jackson MJ, Andree TH, Hansard M, Hoffman DC, Hurtt MR, Kehne JH, Pitler TA, Smith LA, Stack G, and Jenner P (2010) The dopamine D(2) receptor partial agonist aplindore improves motor deficits in MPTP-treated common marmosets alone and combined with L-dopa. *J Neural Transm (Vienna)* **117**:55–67.
- Jackson MJ, Smith LA, Al-Barghouthy G, Rose S, and Jenner P (2007) Decreased expression of l-dopa-induced dyskinesia by switching to ropinirole in MPTP-treated common marmosets. *Exp Neurol* **204**:162–170.
- Jackson MJ, Swart T, Pearce RK, and Jenner P (2014) Cholinergic manipulation of motor disability and L-DOPA-induced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated common marmosets. *J Neural Transm (Vienna)* **121**:163–169.
- Jan C, François C, Tandé D, Yelnik J, Tremblay L, Agid Y, and Hirsch E (2000) Dopaminergic innervation of the pallidum in the normal state, in MPTP-treated monkeys and in parkinsonian patients. *Eur J Neurosci* **12**:4525–4535.
- Jellinger K (1982) Adjuvant treatment of Parkinson's disease with dopamine agonists: open trial with bromocriptine and CU 32-085. *J Neurol* **227**:75–88.
- Jenner P, Rupniak NM, Rose S, Kelly E, Kilpatrick G, Lees A, and Marsden CD (1984) 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in the common marmoset. *Neurosci Lett* **50**:85–90.
- Jenner P, Zeng BY, Smith LA, Pearce RK, Tel B, Chancharme L, and Moachon G (2000) Antiparkinsonian and neuroprotective effects of modafinil in the mptp-treated common marmoset. *Exp Brain Res* **133**:178–188.
- Johnston LC, Jackson MJ, Rose S, McCreary AC, and Jenner P (2010a) Pardoprunox reverses motor deficits but induces only mild dyskinesia in MPTP-treated common marmosets. *Mov Disord* **25**:2059–2066.
- Johnston TH, Fox SH, McIlldowie MJ, Piggott MJ, and Brotchie JM (2010b) Reduction of L-DOPA-induced dyskinesia by the selective metabotropic glutamate receptor 5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. *J Pharmacol Exp Ther* **333**:865–873.
- Johnston TH, Fox SH, Piggott MJ, Savola JM, and Brotchie JM (2010c) The α_2 adrenergic antagonist fipamezole improves quality of levodopa action in Parkinsonian primates. *Mov Disord* **25**:2084–2093.
- Johnston TH, Huot P, Damude S, Fox SH, Jones SW, Rusche JR, and Brotchie JM (2013a) RGFP109, a histone deacetylase inhibitor attenuates L-DOPA-induced dyskinesia in the MPTP-lesioned marmoset: a proof-of-concept study. *Parkinsonism Relat Disord* **19**:260–264.
- Johnston TH, Huot P, Fox SH, Koprich JB, Szeliga KT, James JW, Graef JD, Letchworth SR, Jordan KG, Hill MP, et al. (2013b) TC-8831, a nicotinic acetylcholine receptor agonist, reduces L-DOPA-induced dyskinesia in the MPTP macaque. *Neuropharmacology* **73**:337–347.
- Johnston TH, Huot P, Fox SH, Wakefield JD, Sykes KA, Bartolini WP, Milne GT, Pearson JP, and Brotchie JM (2011) Fatty acid amide hydrolase (FAAH) inhibition reduces L-3,4-dihydroxyphenylalanine-induced hyperactivity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned non-human primate model of Parkinson's disease. *J Pharmacol Exp Ther* **336**:423–430.
- Johnston TH, Millar Z, Huot P, Wagg K, Thiele S, Salomonczyk D, Yong-Kee CJ, Gandy MN, McIlldowie M, Lewis KD, et al. (2012) A novel MDMA analogue, UWA-101, that lacks psychoactivity and cytotoxicity, enhances L-DOPA benefit in parkinsonian primates. *FASEB J* **26**:2154–2163.
- Johnston TH, van der Meij A, Brotchie JM, and Fox SH (2010d) Effect of histamine H2 receptor antagonism on levodopa-induced dyskinesia in the MPTP-macaque model of Parkinson's disease. *Mov Disord* **25**:1379–1390.
- Jones CA, Johnston LC, Jackson MJ, Smith LA, van Scharrenburg G, Rose S, Jenner PG, and McCreary AC (2010) An in vivo pharmacological evaluation of pardoprunox (SLV308)—a novel combined dopamine D(2)/D(3) receptor partial agonist and 5-HT(1A) receptor agonist with efficacy in experimental models of Parkinson's disease. *Eur Neuropsychopharmacol* **20**:582–593.
- Kaakkola S, Teräväinen H, Ahtila S, Rita H, and Gordin A (1994) Effect of entacapone, a COMT inhibitor, on clinical disability and levodopa metabolism in parkinsonian patients. *Neurology* **44**:77–80.
- Kanda T, Jackson MJ, Smith LA, Pearce RK, Nakamura J, Kase H, Kuwana Y, and Jenner P (1998a) Adenosine A2A antagonist: a novel antiparkinsonian agent that does not provoke dyskinesia in parkinsonian monkeys. *Ann Neurol* **43**: 507–513.
- Kanda T, Jackson MJ, Smith LA, Pearce RK, Nakamura J, Kase H, Kuwana Y, and Jenner P (2000) 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* **162**:321–327.
- Kanda T, Tashiro T, Kuwana Y, and Jenner P (1998b) Adenosine A2A receptors modify motor function in MPTP-treated common marmosets. *Neuroreport* **9**: 2857–2860.

- Katzenschlager R, Jackson MJ, Rose S, Stockwell K, Tayarani-Binazir KA, Zubair M, Smith LA, Jenner P, and Lees AJ (2007) Antiparkinsonian activity of L-propyl-L-leucyl-glycinamide or melanocyte-inhibiting factor in MPTP-treated common marmosets. *Mov Disord* **22**:715–719.
- Katzenschlager R, Manson AJ, Evans A, Watt H, and Lees AJ (2004) Low dose quetiapine for drug induced dyskinesias in Parkinson's disease: a double blind cross over study. *J Neurol Neurosurg Psychiatry* **75**:295–297.
- Kebabian JW, Britton DR, DeNinno MP, Perner R, Smith L, Jenner P, Schoenleber R, and Williams M (1992) A-77636: a potent and selective dopamine D1 receptor agonist with antiparkinsonian activity in marmosets. *Eur J Pharmacol* **229**: 203–209.
- Klawans HL and Ringel SP (1973) A clinical study of methysergide in Parkinsonism: evidence against a serotonergic mechanism. *J Neurol Sci* **19**:399–405.
- Klawans HL, Jr and Weiner WJ (1974) Attempted use of haloperidol in the treatment of L-dopa induced dyskinesias. *J Neurol Neurosurg Psychiatry* **37**:427–430.
- Klockgether T, Turski L, Honoré T, Zhang ZM, Gash DM, Kurlan R, and Greenamyre JT (1991) The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. *Ann Neurol* **30**:717–723.
- Ko WK, Li Q, and Bezard E (2014a) Effects of L-tryptophan on L-DOPA-induced dyskinesia in the L-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model of Parkinson's disease. *Neurosci Lett* **566**:72–76.
- Ko WK, Pioli E, Li Q, McGuire S, Dufour A, Sherer TB, Bezard E, and Facheris MF (2014b) Combined fenobam and amantadine treatment promotes robust antidykinetic effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model of Parkinson's disease. *Mov Disord* **29**:772–779.
- Ko WKD, Camus SM, Li Q, Yang J, McGuire S, Pioli EY, and Bezard E (2016) 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* **110** (Pt A):48–58.
- Ko WKD, Li Q, Cheng LY, Morelli M, Carta M, and Bezard E (2017) A preclinical study on the combined effects of repeated eltopazine and preladenant treatment for alleviating L-DOPA-induced dyskinesia in Parkinson's disease. *Eur J Pharmacol* **813**:10–16.
- Kobylecki C, Burn DJ, Kass-Iliyya L, Kellett MW, Crossman AR, and Silverdale MA (2014) Randomized clinical trial of tirapamate for levodopa-induced dyskinesia in Parkinson's disease. *Parkinsonism Relat Disord* **20**:452–455.
- Kobylecki C, Cenci MA, Crossman AR, and Ravenscroft P (2010) Calcium-permeable AMPA receptors are involved in the induction and expression of L-DOPA-induced dyskinesia in Parkinson's disease. *J Neurochem* **114**:499–511.
- Kobylecki C, Hill MP, Crossman AR, and Ravenscroft P (2011) Synergistic antidykinetic effects of tirapamate and amantadine in animal models of Parkinson's disease. *Mov Disord* **26**:2354–2363.
- Koller WC and Herberster G (1987) Adjuvant therapy of parkinsonian tremor. *Arch Neurol* **44**:921–923.
- Konitsiotis S, Blanchet PJ, Verhagen L, Lamers E, and Chase TN (2000) AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys. *Neurology* **54**:1589–1595.
- Koprich JB, Fox SH, Johnston TH, Goodman A, Le Bourdonnec B, Dolle RE, DeHaven RN, DeHaven-Hudkins DL, Little PJ, and Brochie JM (2011) 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* **26**:1225–1233.
- Koprich JB, Huot P, Fox SH, Jarvie K, Lang AE, Seeman P, and Brochie JM (2013) The effects of fast-off-D2 receptor antagonism on L-DOPA-induced dyskinesia and psychosis in parkinsonian macaques. *Prog Neuropsychopharmacol Biol Psychiatry* **43**:151–156.
- Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, and Ruggieri S (1999) A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. *Neurology* **53**:364–370.
- Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, Gironell A, García-Sánchez C, and Martínez-Corral M (2008) Motor changes during sertraline treatment in depressed patients with Parkinson's disease*. *Eur J Neurol* **15**:953–959.
- Lamid S and Jenkins RB (1975) Crossover clinical trial of benapryzine and trihexyphenidyl in Parkinsonian patients. *J Clin Pharmacol* **15**:622–626.
- Lange KW, Löschnann PA, Wachtel H, Horowski R, Jähmig P, Jenner P, and Marsden CD (1992) Terguride stimulates locomotor activity at 2 months but not 10 months after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment of common marmosets. *Eur J Pharmacol* **212**:247–252.
- Langston JW, Ballard P, Tetrad JW, and Irwin I (1983) Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* **219**:979–980.
- Langston JW, Forno LS, Rebert CS, and Irwin I (1984) Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res* **292**:390–394.
- Lees AJ, Lander CM, and Stern GM (1978) Tiapride and sulpiride in Parkinson's disease. *Lancet* **2**:1205.
- Lemay S, Chouinard S, Blanchet P, Masson H, Soland V, Beuter A, and Bédard MA (2004) Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry* **28**: 31–39.
- LeWitt PA, Guttman M, Tetrad JW, Tuite PJ, Mori A, Chaikin P, and Sussman NM; 6002-US-005 Study Group (2008) 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* **63**:295–302.
- Lewitt PA, Hauser RA, Lu M, Nicholas AP, Weiner W, Coppard N, Leinonen M, and Savola JM (2012) Randomized clinical trial of fipamezole for dyskinesia in Parkinson disease (FJORD study). *Neurology* **79**:163–169.
- LeWitt PA, Lyons KE, and Pahwa R; SP 650 Study Group (2007) Advanced Parkinson disease treated with rotigotine transdermal system: PREFER study. *Neurology* **68**:1262–1267.
- Lieberman A, Ranhosky A, and Korts D (1997) Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* **49**:162–168.
- Lieberman AN, Gopinathan G, and Neophytides A (1986) Efficacy of pergolide and mesulergine. *Eur Neurol* **25**:86–90.
- Lincoln L, Fisher R, Jackson MJ, Jenner P, Neumeyer J, Sromek AW, Lees AJ, and Rose S (2016) Oral r(-)-11-o-valeryl-n-n-propylnoraporphine reverses motor deficits in mptp-treated marmosets. *Mov Disord* **31**:1381–1388.
- Lindeboom SF and Lakke JP (1978) Deanol and physostigmine in the treatment of L-dopa-induced dyskinesias. *Acta Neurol Scand* **58**:134–138.
- Löschmann PA, Chong PN, Nomoto M, Tepper PG, Horn AS, Jenner P, and Marsden CD (1989) Stereoselective reversal of MPTP-induced parkinsonism in the marmoset after dermal application of N-0437. *Eur J Pharmacol* **166**:373–380.
- Löschmann PA, De Groote C, Smith L, Wüllner U, Fischer G, Kemp JA, Jenner P, and Klockgether T (2004) Antiparkinsonian activity of Ro 25-6981, a NR2B subunit specific NMDA receptor antagonist, in animal models of Parkinson's disease. *Exp Neurol* **187**:86–93.
- Löschmann PA, Lange KW, Kunow M, Rettig KJ, Jähmig P, Honoré T, Turski L, Wachtel H, Jenner P, and Marsden CD (1991) Synergism of the AMPA-antagonist NBQX and the NMDA-antagonist CPP with L-dopa in models of Parkinson's disease. *J Neural Transm Park Dis Dement Sect* **3**:203–213.
- Löschmann PA, Smith LA, Lange KW, Jähmig P, Jenner P, and Marsden CD (1992) Motor activity following the administration of selective D-1 and D-2 dopaminergic drugs to MPTP-treated common marmosets. *Psychopharmacology (Berl)* **109**: 49–56.
- Luginger E, Wenning GK, Bösch S, and Poewe W (2000) Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord* **15**: 873–878.
- Luquin MR, Laguna J, Herrero MT, and Obeso JA (1993a) Behavioral tolerance to repeated apomorphine administration in parkinsonian monkeys. *J Neurol Sci* **114**: 40–44.
- Luquin MR, Laguna J, and Obeso JA (1992) Selective D2 receptor stimulation induces dyskinesia in parkinsonian monkeys. *Ann Neurol* **31**:551–554.
- Luquin MR, Obeso JA, Laguna J, Guillén J, and Martínez-Lage JM (1993b) The AMPA receptor antagonist NBQX does not alter the motor response induced by selective dopamine agonists in MPTP-treated monkeys. *Eur J Pharmacol* **235**: 297–300.
- Mahmoudi S, Samadi P, Gilbert F, Ouattara B, Morissette M, Grégoire L, Rouillard C, Di Paolo T, and Lévesque D (2009) Nur77 mRNA levels and L-Dopa-induced dyskinesias in MPTP monkeys treated with docosahexaenoic acid. *Neurobiol Dis* **36**:213–222.
- Manson AJ, Iakovidou E, and Lees AJ (2000) Idazoxan is ineffective for levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* **15**:336–337.
- Manson AJ, Katzenschlager R, Hobart J, and Lees AJ (2001) High dose naltrexone for dyskinesias induced by levodopa. *J Neurol Neurosurg Psychiatry* **70**:554–556.
- Maratos EC, Jackson MJ, Pearce RK, Cannizzaro C, and Jenner P (2003) Both short- and long-acting D-1/D-2 dopamine agonists induce less dyskinesia than L-DOPA in the MPTP-lesioned common marmoset (*Callithrix jacchus*). *Exp Neurol* **179**: 90–102.
- Maratos EC, Jackson MJ, Pearce RK, and Jenner P (2001) Antiparkinsonian activity and dyskinesia risk of ropinirole and L-DOPA combination therapy in drug naïve MPTP-lesioned common marmosets (*Callithrix jacchus*). *Mov Disord* **16**:631–641.
- Marino S, Sessa E, Di Lorenzo G, Digangi G, Alagna A, Bramanti P, and Di Bella P (2008) Sertraline in the treatment of depressive disorders in patients with Parkinson's disease. *Neurol Sci* **29**:391–395.
- Marsden CD, Parkes JD, and Rees JE (1973) A year's comparison of treatment of patients with parkinson's disease with levodopa combined with carbidopa versus treatment with levodopa alone. *Lancet* **2**:1459–1462.
- Marti M, Rodi D, Li Q, Guerrini R, Fasano S, Morella I, Tozzi A, Brambilla R, Calabresi P, Simonato M, et al. (2012) Nociceptin/orphanin FQ receptor agonists attenuate L-DOPA-induced dyskinesias. *J Neurosci* **32**:16106–16119.
- Martignoni E, Pachetti C, Aufdembrinke B, Godi L, Albani G, Mancini F, and Nappi G (1995) Terguride in stable Parkinson's disease. *Funct Neurol* **10**:143–146.
- Martin WE, Loewenson RB, Resch JA, and Baker AB (1974) A controlled study comparing trihexyphenidyl hydrochloride plus levodopa with placebo plus levodopa in patients with Parkinson's disease. *Neurology* **24**:912–919.
- McCall RB, Lookingland KJ, Bédard PJ, and Huff RM (2005) Sumanitrole, a highly dopamine D2-selective receptor agonist: in vitro and in vivo pharmacological characterization and efficacy in animal models of Parkinson's disease. *J Pharmacol Exp Ther* **314**:1248–1256.
- Meco G, Fabrizio E, Di Rezze S, Alessandri A, and Pratesi L (2003) Mirtazapine in L-dopa-induced dyskinesias. *Clin Neuropharmacol* **26**:179–181.
- Meltzer HY, Mills R, Revell S, Williams H, Johnson A, Bahr D, and Friedman JH (2010) Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. *Neuropsychopharmacology* **35**:881–892.
- Merello M, Lees AJ, Webster R, Bovingdon M, and Gordin A (1994) Effect of entacapone, a peripherally acting catechol-O-methyltransferase inhibitor, on the motor response to acute treatment with levodopa in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* **57**:186–189.
- Mestre TA, Shah BB, Connolly BS, de Aquino C, Al Dhakeel A, Walsh R, Ghate T, Lui JP, and Fox SH (2014) 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 (Hoboken)* **1**:219–224.
- Millan MJ, Di Cara B, Hill M, Jackson M, Joyce JN, Brochie J, McGuire S, Crossman A, Smith L, Jenner P, et al. (2004) S32504, a novel naphthoxazine agonist at dopamine D3/D2 receptors. II. Actions in rodent, primate, and cellular models of antiparkinsonian activity in comparison to ropinirole. *J Pharmacol Exp Ther* **309**: 921–935.
- Mizuno Y, Kondo T, and Narabayashi H (1995) Pergolide in the treatment of Parkinson's disease. *Neurology* **45**(3 Suppl 3):S13–S21.

- Mizuno Y, Nomoto M, Kondo T, Hasegawa K, Murata M, Takeuchi M, Ikeda J, Tomida T, and Hattori N; Rotigotine Trial Group (2013) Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord* **28**:1447–1450.
- Molinari SP, Kaminski R, Di Rocco A, and Yahr MD (1995) The use of famotidine in the treatment of Parkinson's disease: a pilot study. *J Neural Transm Park Dis Dement Sect* **9**:243–247.
- Montastruc JL, Puech AJ, Clanet M, Guiraud-Chaumeil B, and Rascol A (1981) Yohimbine in treatment of Parkinson's disease: preliminary results (author's transl). *Nouv Presse Med* **10**:1331–1332.
- Montastruc JL, Rascol O, Senard JM, and Rascol A (1994) A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neural Neurosurg Psychiatry* **57**:1034–1038.
- Morin N, Grégoire L, Gomez-Mancilla B, Gasparini F, and Di Paolo T (2010) Effect of the metabotropic glutamate receptor type 5 antagonists MPEP and MTEP in parkinsonian monkeys. *Neuropharmacology* **58**:981–986.
- Morin N, Grégoire L, Morissette M, Desrayaud S, Gomez-Mancilla B, Gasparini F, and Di Paolo T (2013a) MPEP, an mGlu5 receptor antagonist, reduces the development of L-DOPA-induced motor complications in de novo parkinsonian monkeys: biochemical correlates. *Neuropharmacology* **66**:355–364.
- Morin N, Morissette M, Grégoire L, and Di Paolo T (2015a) Effect of a chronic treatment with an mGlu5 receptor antagonist on brain serotonin markers in parkinsonian monkeys. *Prog Neuropsychopharmacol Biol Psychiatry* **56**:27–38.
- Morin N, Morissette M, Grégoire L, Gomez-Mancilla B, Gasparini F, and Di Paolo T (2013b) Chronic treatment with MPEP, an mGlu5 receptor antagonist, normalizes basal ganglia glutamate neurotransmission in L-DOPA-treated parkinsonian monkeys. *Neuropharmacology* **73**:216–231.
- Morin N, Morissette M, Grégoire L, Rajput A, Rajput AH, and Di Paolo T (2015b) Contribution of brain serotonin subtype 1B receptors in levodopa-induced motor complications. *Neuropharmacology* **99**:356–368.
- Morissette M, Dridi M, Calon F, Hadj Tahar A, Meltzer LT, Bédard PJ, and Di Paolo T (2006a) Prevention of dyskinesia by an NMDA receptor antagonist in MPTP monkeys: effect on adenosine A2A receptors. *Synapse* **60**:239–250.
- Morissette M, Dridi M, Calon F, Hadj Tahar A, Meltzer LT, Bédard PJ, and Di Paolo T (2006b) Prevention of levodopa-induced dyskinesias by a selective NR1A/2B N-methyl-D-aspartate receptor antagonist in parkinsonian monkeys: implication of preproenkephalin. *Mov Disord* **21**:9–17.
- Morissette M, Goulet M, Grondin R, Blanchet P, Bédard PJ, Di Paolo T, and Lévesque D (1998) Associative and limbic regions of monkey striatum express high levels of dopamine D3 receptors: effects of MPTP and dopamine agonist replacement therapies. *Eur J Neurosci* **10**:2565–2573.
- Morissette M, Goulet M, Soghomonian JJ, Blanchet PJ, Calon F, Bédard PJ, and Di Paolo T (1997) Preproenkephalin mRNA expression in the caudate-putamen of MPTP monkeys after chronic treatment with the D2 agonist U91356A in continuous or intermittent mode of administration: comparison with L-DOPA therapy. *Brain Res Mol Brain Res* **49**:55–62.
- Morissette M, Grondin R, Goulet M, Bédard PJ, and Di Paolo T (1999) Differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists. *J Neurochem* **72**:682–692.
- Morissette M, Morin N, Grégoire L, Rajput A, Rajput AH, and Di Paolo T (2016) Brain $\alpha 7$ nicotinic acetylcholine receptors in MPTP-lesioned monkeys and parkinsonian patients. *Biochem Pharmacol* **109**:62–69.
- Morissette M, Samadi P, Hadj Tahar A, Bélanger N, and Di Paolo T (2010) Striatal Akt/GSK3 signaling pathway in the development of L-Dopa-induced dyskinesias in MPTP monkeys. *Prog Neuropsychopharmacol Biol Psychiatry* **34**:446–454.
- Muenter MD, Ahlskog JE, Bell G, and McManis P (1988) PHNO [(+)-4-propyl-9-hydroxynaphthoxazine]: a new and effective anti-Parkinson's disease agent. *Neurology* **38**:1541–1545.
- Muñoz A, Li Q, Gardoni F, Marcello E, Qin C, Carlsson T, Kirik D, Di Luca M, Björklund A, Bezard E, et al. (2008) Combined 5-HT1A and 5-HT1B receptor agonists for the treatment of L-DOPA-induced dyskinesia. *Brain* **131**:3380–3394.
- Nagata T, Shinagawa S, Tagai K, and Nakayama K (2013) A case in which mirtazapine reduced auditory hallucinations in a patient with Parkinson disease. *Int Psychogeriatr* **25**:1199–1201.
- Nash JE, Fox SH, Henry B, Hill MP, Peggs D, McGuire S, Maneuf Y, Hille C, Brochie JM, and Crossman AR (2000) Antiparkinsonian actions of ifenprodil in the MPTP-lesioned marmoset model of Parkinson's disease. *Exp Neurol* **165**:136–142.
- Nash JE, Ravenscroft P, McGuire S, Crossman AR, Menniti FS, and Brochie JM (2004) 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* **188**:471–479.
- NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators (2015) Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. *Lancet Neurol* **14**:795–803.
- Nomoto M, Jenner P, and Marsden CD (1985) The dopamine D2 agonist LY 171866, but not the D1 agonist SKF 38393, reverses parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset. *Neurosci Lett* **57**:37–41.
- Nomoto M, Jenner P, and Marsden CD (1988) The D1 agonist SKF 38393 inhibits the antiparkinsonian activity of the D2 agonist LY 171555 in the MPTP-treated marmoset. *Neurosci Lett* **93**:275–280.
- Nomoto M, Stahl S, Jenner P, and Marsden CD (1987) Antiparkinsonian activity of (+)-PHNO in the MPTP-treated common marmoset. *Mov Disord* **2**:37–45.
- Nutt JG, Gunzler SA, Kirchhoff T, Hogarth P, Weaver JL, Krams M, Jamerson B, Menniti FS, and Landen JW (2008) Effects of a NR2B selective NMDA glutamate antagonist, CP-101,606, on dyskinesia and Parkinsonism. *Mov Disord* **23**:1860–1866.
- Oertel W, Eggert K, Pahwa R, Tanner CM, Hauser RA, Trenkwalder C, Ehret R, Azulay JP, Isaacson S, Felt L, et al. (2017) Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord* **31**:1701–1709.
- Oertel WH, Wolters E, Sampaio C, Gimenez-Roldan S, Bergamasco B, Dujardin M, Grosset DG, Arnold G, Leenders KL, Hundemer HP, et al. (2006) Pergolide versus levodopa monotherapy in early Parkinson's disease patients: the PELMOPET study. *Mov Disord* **21**:343–353.
- Oh JD, Bibbiani F, and Chase TN (2002) Quetiapine attenuates levodopa-induced motor complications in rodent and primate parkinsonian models. *Exp Neurol* **177**:557–564.
- Olanow CW, Damier P, Goetz CG, Mueller T, Nutt J, Rascol O, Serbanescu A, Deckers F, and Russ H (2004) Multicenter, open-label, trial of sarizotan in Parkinson disease patients with levodopa-induced dyskinesias (the SPLENDID study). *Clin Neuropharmacol* **27**:58–62.
- Olanow CW, Fahn S, Muenter M, Klawans H, Hurtig H, Stern M, Shoulson I, Kurlan R, Grimes JD, Jankovic J, et al. (1994) A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Mov Disord* **9**:40–47.
- Ondo WG, Tintner R, Young KD, Lai D, and Ringholz G (2005) Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. *Mov Disord* **20**:958–963.
- Ouattara B, Belkhir S, Morissette M, Dridi M, Samadi P, Grégoire L, Meltzer LT, and Di Paolo T (2009) Implication of NMDA receptors in the antidykinetic activity of cabergoline, CI-1041, and Ro 61-8048 in MPTP monkeys with levodopa-induced dyskinesias. *J Mol Neurosci* **38**:128–142.
- Ouattara B, Grégoire L, Morissette M, Gasparini F, Vranesic I, Bilbe G, Johns DR, Rajput A, Hornykiewicz O, Rajput AH, et al. (2011) Metabotropic glutamate receptor type 5 in levodopa-induced motor complications. *Neurobiol Aging* **32**:1286–1295.
- Ouattara B, Hoyer D, Grégoire L, Morissette M, Gasparini F, Gomez-Mancilla B, and Di Paolo T (2010) Changes of AMPA receptors in MPTP monkeys with levodopa-induced dyskinesias. *Neuroscience* **167**:1160–1167.
- Pahwa R, Tanner CM, Hauser RA, Isaacson SH, Nausieda PA, Truong DD, Agarwal P, Hull KL, Lyons KE, Johnson R, et al. (2017) ADS-5102 (Amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): a randomized clinical trial. *JAMA Neurol* **74**:941–949.
- Pålhagen SE, Carlsson M, Curman E, Wälinder J, and Granérus AK (2008) Depressive illness in Parkinson's disease—indication of a more advanced and widespread neurodegenerative process? *Acta Neurol Scand* **117**:295–304.
- Pålhagen SE, Ekberg S, Wälinder J, Granérus AK, and Granerus G (2009) HMPAO SPECT in Parkinson's disease (PD) with major depression (MD) before and after antidepressant treatment. *J Neurol* **256**:1510–1518.
- Papa SM, Auberson JP, and Greenamyre JT (2004) Prolongation of levodopa responses by glycineB antagonists in parkinsonian primates. *Ann Neurol* **56**:723–727.
- Papa SM and Chase TN (1996) Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys. *Ann Neurol* **39**:574–578.
- Park DM, Findley LJ, Hanks G, and Sandler M (1981) Nomifensine: effect in Parkinsonian patients not receiving levodopa. *J Neurol Neurosurg Psychiatry* **44**:352–354.
- Park DM, Findley LJ, and Teychenne PF (1977) Nomifensine in parkinsonism. *Br J Clin Pharmacol* (4 Suppl 2):185S–186S.
- Parkes JD, Baxter RC, Curzon G, Knill-Jones RP, Knott PJ, Marsden CD, Tattersall R, and Vollum D (1971) Treatment of Parkinson's disease with amantadine and levodopa: a one-year study. *Lancet* **1**:1083–1086.
- Parkinson Study Group (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* **340**:757–763.
- Parkinson Study Group (2000a) A multicenter randomized controlled trial of remacemide hydrochloride as monotherapy for PD. *Neurology* **54**:1583–1588.
- Parkinson Study Group (2000b) Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* **284**:1931–1938.
- Parkinson Study Group (2001) Evaluation of dyskinesias in a pilot, randomized, placebo-controlled trial of remacemide in advanced Parkinson disease. *Arch Neurol* **58**:1660–1668.
- Parkinson Study Group (2003) A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol* **60**:1721–1728.
- Parkinson Study Group (2005) A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* **62**:241–248.
- Pearce RK, Banerji T, Jenner P, and Marsden CD (1998) De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in the MPTP-treated marmoset. *Mov Disord* **13**:234–241.
- Pearce RK, Jackson M, Britton DR, Shiosaki K, Jenner P, and Marsden CD (1999) Actions of the D1 agonists A-77636 and A-86929 on locomotion and dyskinesia in MPTP-treated L-dopa-primed common marmosets. *Psychopharmacology (Berl)* **142**:51–60.
- Pearce RK, Jackson M, Smith L, Jenner P, and Marsden CD (1995) Chronic L-DOPA administration induces dyskinesias in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated common marmoset (*Callithrix jacchus*). *Mov Disord* **10**:731–740.
- Pearce RK, Smith LA, Jackson MJ, Banerji T, Scheel-Krüger J, and Jenner P (2002) The monoamine reuptake blocker brafosensine reverses akinesia without dyskinesia in MPTP-treated and levodopa-primed common marmosets. *Mov Disord* **17**:877–886.
- Pessiglione M, Guehl D, Hirsch EC, Féger J, and Tremblay L (2004a) Disruption of self-organized actions in monkeys with progressive MPTP-induced parkinsonism. I. Effects of task complexity. *Eur J Neurosci* **19**:426–436.
- Pessiglione M, Guehl D, Jan C, François C, Hirsch EC, Féger J, and Tremblay L (2004b) Disruption of self-organized actions in monkeys with progressive MPTP-induced parkinsonism: II. Effects of reward preference. *Eur J Neurosci* **19**:437–446.

- Philippens IH, Joosen MJ, Ahnaou A, Andres I, and Drinkenburg WP (2014) Anti-Parkinson effects of a selective alpha2C-adrenoceptor antagonist in the MPTP marmoset model. *Behav Brain Res* **269**:81–86.
- Pinna A, Ko WK, Costa G, Tronci E, Fidalgo C, Simola N, Li Q, Tabrizi MA, Bezard E, Carta M, et al. (2016) Antidyskinetic effect of A2A and 5HT1A/1B receptor ligands in two animal models of Parkinson's disease. *Mov Disord* **31**:501–511.
- Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, Rupp M, and Boroojerdi B; SP 515 Investigators (2007) Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol* **6**:513–520.
- Porras G, Li Q, and Bezard E (2012) Modeling Parkinson's disease in primates: the MPTP model. *Cold Spring Harb Perspect Med* **2**:a009308.
- Potts LF, Park ES, Woo JM, Dyavar Shetty BL, Singh A, Braithwaite SP, Voronkov M, Papa SM, and Mouradian MM (2015) Dual κ -agonist/ μ -antagonist opioid receptor modulation reduces levodopa-induced dyskinesia and corrects dysregulated striatal changes in the nonhuman primate model of Parkinson disease. *Ann Neurol* **77**:930–941.
- Pourcher E, Bonnet AM, Kefalos J, Dubois B, and Agid Y (1989) Effects of etybenzatropine and diazepam on levodopa-induced diphasic dyskinesias in Parkinson's disease. *Mov Disord* **4**:195–201.
- Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, and Chaikin P (2012) Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the KW-6002-US-018 study. *Parkinsonism Relat Disord* **18**:178–184.
- Pourcher E, Gomez-Mancilla B, and Bédard PJ (1992) Ethosuximide and tremor in Parkinson's disease: a pilot study. *Mov Disord* **7**:132–136.
- Quik M, Cox H, Parameswaran N, O'Leary K, Langston JW, and Di Monte D (2007) Nicotine reduces levodopa-induced dyskinesias in lesioned monkeys. *Ann Neurol* **62**:588–596.
- Quik M, Mallela A, Chin M, McIntosh JM, Perez XA, and Bordia T (2013a) Nicotine-mediated improvement in L-dopa-induced dyskinesias in MPTP-lesioned monkeys is dependent on dopamine nerve terminal function. *Neurobiol Dis* **50**:30–41.
- Quik M, Mallela A, Ly J, and Zhang D (2013b) Nicotine reduces established levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Mov Disord* **28**:1398–1406.
- Quinn N, Illas A, Lhermitte F, and Agid Y (1981) Bromocriptine and domperidone in the treatment of Parkinson disease. *Neurology* **31**:662–667.
- Rampello L, Chiechio S, Raffaele R, Vecchio I, and Nicoletti F (2002) The SSRI, citalopram, improves bradykinesia in patients with Parkinson's disease treated with L-dopa. *Clin Neuropharmacol* **25**:21–24.
- Rascol O, Arnulf I, Peyro-Saint Paul H, Brefel-Courbon C, Vidailhet M, Thalamas C, Bonnet AM, Descombes S, Bejjani B, Fabre N, et al. (2001a) Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease. *Mov Disord* **16**:708–713.
- Rascol O, Blin O, Thalamas C, Descombes S, Soubrouillard C, Azulay P, Fabre N, Viallet F, Lafnitzegger K, Wright S, et al. (1999) ABT-431, a D1 receptor agonist prodrug, has efficacy in Parkinson's disease. *Ann Neurol* **45**:736–741.
- Rascol O, Bronzova J, Hauser RA, Lang AE, Sampaio C, Theeuwes A, and van de Witte SV (2012) Pardoprunox as adjunct therapy to levodopa in patients with Parkinson's disease experiencing motor fluctuations: results of a double-blind, randomized, placebo-controlled, trial. *Parkinsonism Relat Disord* **18**:370–376.
- Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, and Lang AE (2000) A five-year study of the incidence of dyskinesias in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* **342**:1484–1491.
- Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE, and Abdalla M; 056 Study Group (2006a) Development of dyskinesias in a 5-year trial of ropinirole and L-dopa. *Mov Disord* **21**:1844–1850.
- Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, and Tolosa E; LARGO study group (2005) Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, lasting effect in adjunct therapy with rasagiline given once daily, study): a randomised, double-blind, parallel-group trial. *Lancet* **365**:947–954.
- Rascol O, Dubois B, Caldas AC, Senn S, Del Signore S, and Lees A; Parkinson REGAIN Study Group (2006b) Early piribedil monotherapy of Parkinson's disease: a planned seven-month report of the REGAIN study. *Mov Disord* **21**:2110–2115.
- Rascol O, Fabre N, Blin O, Poulik J, Sabatini U, Senard JM, Ané M, Montastruc JL, and Rascol A (1994) Naltrexone, an opiate antagonist, fails to modify motor symptoms in patients with Parkinson's disease. *Mov Disord* **9**:437–440.
- Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, and Fuell D (1996) Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Clin Neuropharmacol* **19**:234–245.
- Rascol O, Nutt JG, Blin O, Goetz CG, Trugman JM, Soubrouillard C, Carter JH, Currie LJ, Fabre N, Thalamas C, et al. (2001b) Induction by dopamine D1 receptor agonist ABT-431 of dyskinesia similar to levodopa in patients with Parkinson disease. *Arch Neurol* **58**:249–254.
- Riahi G, Morissette M, Lévesque D, Rouillard C, Samadi P, Parent M, and Di Paolo T (2012) Effect of chronic L-DOPA treatment on 5-HT(1A) receptors in parkinsonian monkey brain. *Neurochem Int* **61**:1160–1171.
- Riahi G, Morissette M, Parent M, and Di Paolo T (2011) Brain 5-HT(2A) receptors in MPTP monkeys and levodopa-induced dyskinesias. *Eur J Neurosci* **33**:1823–1831.
- Riahi G, Morissette M, Samadi P, Parent M, and Di Paolo T (2013) Basal ganglia serotonin 1B receptors in parkinsonian monkeys with L-DOPA-induced dyskinesia. *Biochem Pharmacol* **86**:970–978.
- Rinne UK, Birket-Smith E, Dupont E, Hansen E, Hyyppä M, Marttila R, Mikkelsen B, Pakkenberg H, and Presthus J (1975) Levodopa alone and in combination with a peripheral decarboxylase inhibitor benserazide (Madopar) in the treatment of Parkinson's disease: a controlled clinical trial. *J Neurol* **211**:1–9.
- Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Marti Masso JF, Montastruc JL, Marsden CD, Dubini A, Orlando N, et al. (1997) Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 collaborative study group. *Neurology* **48**:363–368.
- Rose S, Jackson MJ, Smith LA, Stockwell K, Johnson L, Carminati P, and Jenner P (2006) 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* **546**:82–87.
- Rose S, Scheller DK, Breidenbach A, Smith L, Jackson M, Stockwell K, and Jenner P (2007) Plasma levels of rotigotine and the reversal of motor deficits in MPTP-treated primates. *Behav Pharmacol* **18**:155–160.
- Rouillard C, Bédard PJ, and Di Paolo T (1990) Effects of chronic treatment of MPTP monkeys with bromocriptine alone or in combination with SKF 38393. *Eur J Pharmacol* **185**:209–215.
- Rylander D, Iderberg H, Li Q, Dekundy A, Zhang J, Li H, Baishen R, Danysz W, Bezard E, and Cenci MA (2010) A mGluR5 antagonist under clinical development improves L-DOPA-induced dyskinesia in parkinsonian rats and monkeys. *Neurobiol Dis* **39**:352–361.
- Samadi P, Grégoire L, and Bédard PJ (2003) Opioid antagonists increase the dyskinetic response to dopaminergic agents in parkinsonian monkeys: interaction between dopamine and opioid systems. *Neuropharmacology* **45**:954–963.
- Samadi P, Grégoire L, and Bédard PJ (2004) The opioid agonist morphine decreases the dyskinetic response to dopaminergic agents in parkinsonian monkeys. *Neurobiol Dis* **16**:246–253.
- Samadi P, Grégoire L, Hadj Tahar A, Di Paolo T, Rouillard C, and Bédard PJ (2005a) Naltrexone in the short-term decreases antiparkinsonian response to L-Dopa and in the long-term increases dyskinesias in drug-naïve parkinsonian monkeys. *Neuropharmacology* **49**:165–173.
- Samadi P, Grégoire L, Morissette M, Calon F, Hadj Tahar A, Bélanger N, Dridi M, Bédard PJ, and Di Paolo T (2008a) Basal ganglia group II metabotropic glutamate receptors specific binding in non-human primate model of L-Dopa-induced dyskinesias. *Neuropharmacology* **54**:258–268.
- Samadi P, Grégoire L, Morissette M, Calon F, Hadj Tahar A, Dridi M, Belanger N, Meltzer LT, Bédard PJ, and Di Paolo T (2008b) mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys. *Neurobiol Aging* **29**:1040–1051.
- Samadi P, Grégoire L, Rassoulpour A, Guidetti P, Izzo E, Schwarcz R, and Bédard PJ (2005b) Effect of kynurenic acid 3-hydroxylase inhibition on the dyskinetic and anti-parkinsonian responses to levodopa in Parkinsonian monkeys. *Mov Disord* **20**:792–802.
- Samadi P, Grégoire L, Rouillard C, and Bédard PJ (2005c) Dyskinesias occur in response to saline and naltrexone alone after priming with combination of dopaminergic agents and naltrexone in the MPTP parkinsonian monkeys. *Neurobiol Dis* **19**:266–272.
- Samadi P, Grégoire L, Rouillard C, Bédard PJ, Di Paolo T, and Lévesque D (2006) Docosahexaenoic acid reduces levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys. *Ann Neurol* **59**:282–288.
- Samadi P, Morissette M, Calon F, Hadj Tahar A, Dridi M, Belanger N, Meltzer LT, Bédard PJ, and Di Paolo T (2008c) Normalization of GABAA receptor specific binding in the substantia nigra reticulata and the prevention of L-dopa-induced dyskinesias in MPTP parkinsonian monkeys. *Synapse* **62**:101–109.
- Samadi P, Morissette M, Lévesque D, and Di Paolo T (2010) BDNF levels are not related with levodopa-induced dyskinesias in MPTP monkeys. *Mov Disord* **25**:116–121.
- Sampaio C, Bronzova J, Hauser RA, Lang AE, Rascol O, van de Witte SV, and Theeuwes AA; Rembrandt/Vermeer Study Groups (2011) Pardoprunox in early Parkinson's disease: results from 2 large, randomized double-blind trials. *Mov Disord* **26**:1464–1476.
- Savola JM, Hill M, Engstrom M, Merivuori H, Wurster S, McGuire SG, Fox SH, Crossman AR, and Brotchie JM (2003) Fipamezole (JP-1730) is a potent alpha2 adrenergic receptor antagonist that reduces levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. *Mov Disord* **18**:872–883.
- Schapiro AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, and Anand R (2017) Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol* **74**:216–224.
- Schwab RS, Amadori LV, and Lettvin JY (1951) Apomorphine in Parkinson's disease. *Trans Am Neurol Assoc* **56**:251–253.
- Serrano-Dueñas M (2000) Acute pharmacological test with clonidine for the tremor in patients with Parkinson disease. *Rev Neurol* **30**:910–913.
- Shen W, Plotkin JL, Francardo V, Ko WK, Xie Z, Li Q, Fieblinger T, Wess J, Neubig RR, Lindsley CW, et al. (2015) M4 muscarinic receptor signaling ameliorates striatal plasticity deficits in models of L-DOPA-induced dyskinesia. *Neuron* **88**:762–773.
- Shiosaki K, Jenner P, Asin KE, Britton DR, Lin CW, Michaelides M, Smith L, Bianchi B, Didomenico S, Hodges L, et al. (1996) ABT-431: the diacyetyl prodrug of A-86929, a potent and selective dopamine D1 receptor agonist: in vitro characterization and effects in animal models of Parkinson's disease. *J Pharmacol Exp Ther* **276**:150–160.
- Shoulson I and Chase TN (1976) Clonidine and the anti-parkinsonian response to L-DOPA or piribedil. *Neuropharmacology* **15**:25–27.
- Shoulson I, Penney J, McDermott M, Schwid S, Kayson E, Chase T, Fahn S, Greenamyre JT, Lang A, Siderowf A, et al.; Parkinson Study Group (2001) A randomized, controlled trial of remacemide for motor fluctuations in Parkinson's disease. *Neurology* **56**:455–462.
- Sieradzka KA, Fox SH, Hill M, Dick JP, Crossman AR, and Brotchie JM (2001) Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. *Neurology* **57**:2108–2111.
- Silverdale MA, Crossman AR, and Brotchie JM (2002) Striatal AMPA receptor binding is unaltered in the MPTP-lesioned macaque model of Parkinson's disease and dyskinesia. *Exp Neurol* **174**:21–28.

- Silverdale MA, Nicholson SL, Crossman AR, and Brochie JM (2005) Topiramate reduces levodopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease. *Mov Disord* **20**:403–409.
- Silverdale MA, Nicholson SL, Ravenscroft P, Crossman AR, Millan MJ, and Brochie JM (2004) Selective blockade of D(3) dopamine receptors enhances the anti-parkinsonian properties of ropinirole and levodopa in the MPTP-lesioned primate. *Exp Neurol* **188**:128–138.
- Singer C, Lamb J, Ellis A, and Layton G; Sumanrole for Early Parkinson's Disease Study Group (2007) A comparison of sumanirole versus placebo or ropinirole for the treatment of patients with early Parkinson's disease. *Mov Disord* **22**:476–482.
- Smith CP, Oh JD, Bibbiani F, Collins MA, Avila I, and Chase TN (2007) Tamoxifen effect on L-DOPA induced response complications in parkinsonian rats and primates. *Neuropharmacology* **52**:515–526.
- Smith L, De Salvia M, Jenner P, and Marsden CD (1996) An appraisal of the anti-parkinsonian activity of piribedil in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated common marmosets. *Mov Disord* **11**:125–135.
- Smith LA, Gordin A, Jenner P, and Marsden CD (1997) Entacapone enhances levodopa-induced reversal of motor disability in MPTP-treated common marmosets. *Mov Disord* **12**:935–945.
- Smith LA, Jackson MG, Bonhomme C, Chezaubernard C, Pearce RK, and Jenner P (2000) Transdermal administration of piribedil reverses MPTP-induced motor deficits in the common marmoset. *Clin Neuropharmacol* **23**:133–142.
- Smith LA, Jackson MJ, Al-Barghouthy G, and Jenner P (2002a) The actions of a D-1 agonist in MPTP treated primates show dependence on both D-1 and D-2 receptor function and tolerance on repeated administration. *J Neural Transm (Vienna)* **109**:123–140.
- Smith LA, Jackson MJ, Al-Barghouthy G, Rose S, Kuoppamaki M, Olanow W, and Jenner P (2005) Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naïve primates. *Mov Disord* **20**:306–314.
- Smith LA, Jackson MJ, Hansard MJ, Maratos E, and Jenner P (2003) Effect of pulsatile administration of levodopa on dyskinesia induction in drug-naïve MPTP-treated common marmosets: effect of dose, frequency of administration, and brain exposure. *Mov Disord* **18**:487–495.
- Smith LA, Jackson MJ, Johnston L, Kuoppamaki M, Rose S, Al-Barghouthy G, Del Signore S, and Jenner P (2006) Switching from levodopa to the long-acting dopamine D2/D3 agonist piribedil reduces the expression of dyskinesia while maintaining effective motor activity in MPTP-treated primates. *Clin Neuropharmacol* **29**:112–125.
- Smith LA, Tel BC, Jackson MJ, Hansard MJ, Bracerar R, Bonhomme C, Chezaubernard C, Del Signore S, Rose S, and Jenner P (2002b) Repeated administration of piribedil induces less dyskinesia than L-dopa in MPTP-treated common marmosets: a behavioural and biochemical investigation. *Mov Disord* **17**:887–901.
- Soghomonian JJ, Pedneault S, Audet G, and Parent A (1994) Increased glutamate decarboxylase mRNA levels in the striatum and pallidum of MPTP-treated primates. *J Neurosci* **14**:6256–6265.
- Stathis P, Konitsiotis S, Tagaris G, and Peterson D; VALID-PD Study Group (2011) Levitracetam for the management of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* **26**:264–270.
- Steece-Collier K, Chambers LK, Jaw-Tsai SS, Menniti FS, and Greenamyre JT (2000) Antiparkinsonian actions of CP-101,606, an antagonist of NR2B subunit-containing N-methyl-D-aspartate receptors. *Exp Neurol* **163**:239–243.
- Stibe C, Lees A, and Stern G (1987) Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. *Lancet* **1**:871.
- Stocchi F, Rascol O, Destee A, Hattori N, Hauser RA, Lang AE, Poewe W, Stacy M, Tolosa E, Gao H, et al. (2013) AFQ056 in Parkinson patients with levodopa-induced dyskinesia: 13-week, randomized, dose-finding study. *Mov Disord* **28**:1838–1846.
- Stocchi F, Rascol O, Hauser RA, Huyck S, Tzontcheva A, Capece R, Ho TW, Sklar P, Lines C, Michelson D, et al.; Preladenant Early Parkinson Disease Study Group (2017) Randomized trial of preladenant, given as monotherapy, in patients with early Parkinson disease. *Neurology* **88**:2198–2206.
- Stockwell KA, Scheller D, Rose S, Jackson MJ, Tayarani-Binazir K, Iravani MM, Smith LA, Olanow CW, and Jenner P (2009) Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction. *Exp Neurol* **219**:533–542.
- Stockwell KA, Scheller DK, Smith LA, Rose S, Iravani MM, Jackson MJ, and Jenner P (2010) Continuous rotigotine administration reduces dyskinesia resulting from pulsatile treatment with rotigotine or L-DOPA in MPTP-treated common marmosets. *Exp Neurol* **221**:79–85.
- Stockwell KA, Virley DJ, Perren M, Iravani MM, Jackson MJ, Rose S, and Jenner P (2008) Continuous delivery of ropinirole reverses motor deficits without dyskinesia induction in MPTP-treated common marmosets. *Exp Neurol* **211**:172–179.
- Stoessl AJ, Mak E, and Calne DB (1985) (+)-4-Propyl-9-hydroxynaphthoxazine (PHNO), a new dopaminomimetic, in treatment of parkinsonism. *Lancet* **2**:1330–1331.
- Svenningsson P, Rosenblad C, Af Edholm Arvidsson K, Victorin K, Keywood C, Shankar B, Lowe DA, Björklund A, and Widner H (2015) Eltopazine counteracts L-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study. *Brain* **138**:963–973.
- Tagai K, Nagata T, Shinagawa S, Tsuno N, Ozone M, and Nakayama K (2013) Mirtazapine improves visual hallucinations in Parkinson's disease: a case report. *Psychogeriatrics* **13**:103–107.
- Tamim MK, Samadi P, Morissette M, Grégoire L, Ouattara B, Lévesque D, Rouillard C, and Di Paolo T (2010) Effect of non-dopaminergic drug treatment on Levodopa induced dyskinesias in MPTP monkeys: common implication of striatal neuropeptides. *Neuropharmacology* **58**:286–296.
- Tarsy D, Leopold N, and Sax DS (1974) Physostigmine in choreiform movement disorders. *Neurology* **24**:28–33.
- Tayarani-Binazir K, Jackson MJ, Rose S, McCreary AC, and Jenner P (2010a) The partial dopamine agonist pardoprunox (SLV308) administered in combination with l-dopa improves efficacy and decreases dyskinesia in MPTP treated common marmosets. *Exp Neurol* **226**:320–327.
- Tayarani-Binazir KA, Jackson MJ, Rose S, Olanow CW, and Jenner P (2010b) Pramipexole combined with levodopa improves motor function but reduces dyskinesia in MPTP-treated common marmosets. *Mov Disord* **25**:377–384.
- Temlett JA, Chong PN, Oertel WH, Jenner P, and Marsden CD (1988) The D-1 dopamine receptor partial agonist, CY 208-243, exhibits antiparkinsonian activity in the MPTP-treated marmoset. *Eur J Pharmacol* **156**:197–206.
- Temlett JA, Quinn NP, Jenner PG, Marsden CD, Pourcher E, Bonnet AM, Agid Y, Markstein R, and Lataste X (1989) Antiparkinsonian activity of CY 208-243, a partial D-1 dopamine receptor agonist, in MPTP-treated marmosets and patients with Parkinson's disease. *Mov Disord* **4**:261–265.
- Teychenne PF, Park DM, Findley LJ, Rose FC, and Calne DB (1976) Nomifensine in parkinsonism. *J Neurol Neurosurg Psychiatry* **39**:1219–1221.
- Tison F, Keywood C, Wakefield M, Durif F, Corvol JC, Eggert K, Lew M, Isaacson S, Bezdard E, Poli SM, et al. (2016) A phase 2A trial of the novel mGluR5-negative allosteric modulator dipraglurant for levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord* **31**:1373–1380.
- Tison F, Nègre-Pagès L, Meissner WG, Dupouy S, Li Q, Thiolat ML, Thiollier T, Galitzky M, Ory-Magne F, Milhet A, et al. (2013) Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. *Parkinsonism Relat Disord* **19**:416–421.
- Trabucchi M, Bassi S, and Frattola L (1982) Effect of naloxone on the "on-off" syndrome in patients receiving long-term levodopa therapy. *Arch Neurol* **39**:120–121.
- Trenkwalder C, Berg D, Rascol O, Eggert K, Ceballos-Baumann A, Corvol JC, Storch A, Zhang L, Azulay JP, Broussolle E, et al. (2016a) A placebo-controlled trial of AQW051 in patients with moderate to severe levodopa-induced dyskinesia. *Mov Disord* **31**:1049–1054.
- Trenkwalder C, Stocchi F, Poewe W, Dronamraju N, Kenney C, Shah A, von Raison F, and Graf A (2016b) Mavoglurant in Parkinson's patients with l-dopa-induced dyskinesias: two randomized phase 2 studies. *Mov Disord* **31**:1054–1058.
- Treseder SA, Jackson M, and Jenner P (2000) The effects of central aromatic amino acid DOPA decarboxylase inhibition on the motor actions of L-DOPA and dopamine agonists in MPTP-treated primates. *Br J Pharmacol* **129**:1355–1364.
- Tsui JK, Wolters EC, Peppard RF, and Calne DB (1989) A double-blind, placebo-controlled, dose-ranging study to investigate the safety and efficacy of CY 208-243 in patients with Parkinson's disease. *Neurology* **39**:856–858.
- Tyne H, Brooks J, Taylor J, Vinjamuri S, Baker G, and Steiger M (2007) A double blind placebo controlled study of modafinil for Parkinson's disease related fatigue. *Parkinsonism Relat Disord* **13** (Suppl 2):S113–S114.
- Tyne HL, Taylor J, Baker GA, and Steiger MJ (2010) Modafinil for Parkinson's disease fatigue. *J Neurol* **257**:452–456.
- Uchida S, Soshiroda K, Okita E, Kawai-Uchida M, Mori A, Jenner P, and Kanda T (2015a) The adenosine A2A receptor antagonist, istradefylline enhances anti-parkinsonian activity induced by combined treatment with low doses of L-DOPA and dopamine agonists in MPTP-treated common marmosets. *Eur J Pharmacol* **766**:25–30.
- Uchida S, Soshiroda K, Okita E, Kawai-Uchida M, Mori A, Jenner P, and Kanda T (2015b) The adenosine A2A receptor antagonist, istradefylline enhances the anti-parkinsonian activity of low doses of dopamine agonists in MPTP-treated common marmosets. *Eur J Pharmacol* **747**:160–165.
- Uchida S, Tashiro T, Kawai-Uchida M, Mori A, Jenner P, and Kanda T (2014) Adenosine A2A-receptor antagonist istradefylline enhances the motor response of L-DOPA without worsening dyskinesia in MPTP-treated common marmosets. *J Pharmacol Sci* **124**:480–485.
- van der Stelt M, Fox SH, Hill M, Crossman AR, Petrosino S, Di Marzo V, and Brochie JM (2005) A role for endocannabinoids in the generation of parkinsonism and levodopa-induced dyskinesia in MPTP-lesioned non-human primate models of Parkinson's disease. *FASEB J* **19**:1140–1142.
- van Vliet SA, Vanwersch RA, Jongsma MJ, Olivier B, and Philippens IH (2008) Therapeutic effects of Delta9-THC and modafinil in a marmoset Parkinson model. *Eur Neuropsychopharmacol* **18**:383–389.
- Vanover KE, Betz AJ, Weber SM, Bibbiani F, Kiehlaita A, Weiner DM, Davis RE, Chase TN, and Salamone JD (2008) 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* **90**:540–544.
- Verhagen Metman L, Del Dotto P, van den Munkhof P, Fang J, Mouradian MM, and Chase TN (1998) Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology* **50**:1323–1326.
- Vermeulen RJ, Drukarch B, Sahadat MC, Goosen C, Schoffeleer AN, Wolters EC, and Stoof JC (1995) Morphine and naltrexone modulate D2 but not D1 receptor induced motor behavior in MPTP-lesioned monkeys. *Psychopharmacology (Berl)* **118**:451–459.
- Viergege A, Sieberer M, Jacobs H, Hagenah JM, and Viergege P (2001) Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. *Neurology* **57**:1023–1035.
- Villafane G, Cesaro P, Rialland A, Baloul S, Azimi S, Bourdet C, Le Houezec J, Macquin-Mavier I, and Maison P (2007) Chronic high dose transdermal nicotine in Parkinson's disease: an open trial. *Eur J Neurol* **14**:1313–1316.
- Visanji NP, de Bie RM, Johnston TH, McCreary AC, Brochie JM, and Fox SH (2008) The nociceptin/orphanin FQ (NOP) receptor antagonist J-113397 enhances the effects of levodopa in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* **23**:1922–1925.
- Visanji NP, Fox SH, Johnston T, Reyes G, Millan MJ, and Brochie JM (2009a) Dopamine D3 receptor stimulation underlies the development of L-DOPA-induced dyskinesia in animal models of Parkinson's disease. *Neurobiol Dis* **35**:184–192.
- Visanji NP, Fox SH, Johnston TH, Millan MJ, and Brochie JM (2009b) Alpha1-adrenoceptors mediate dihydroxyphenylalanine-induced activity in

- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaques. *J Pharmacol Exp Ther* **328**:276–283.
- Visanji NP, Gomez-Ramirez J, Johnston TH, Pires D, Voon V, Brotchie JM, and Fox SH (2006) Pharmacological characterization of psychosis-like behavior in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* **21**: 1879–1891.
- Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, and Lang AE (2010) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* **67**: 589–595.
- Wolz M, Löhle M, Strecker K, Schwanebeck U, Schneider C, Reichmann H, Grählert X, Schwarz J, and Storch A (2010) Levodopa-induced dyskinesia in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *J Neural Transm (Vienna)* **117**:1279–1286.
- Wong KK, Alty JE, Goy AG, Raghav S, Reutens DC, and Kempster PA (2011) A randomized, double-blind, placebo-controlled trial of levetiracetam for dyskinesia in Parkinson's disease. *Mov Disord* **26**:1552–1555.
- Wright A, Lees AJ, and Stern GM (1987) Mesulergine and pergolide in previously untreated Parkinson's disease. *J Neurol Neurosurg Psychiatry* **50**:482–484.
- Yan T, Rizak JD, Yang S, Li H, Huang B, Ma Y, and Hu X (2014) Acute morphine treatments alleviate tremor in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys. *PLoS One* **9**:e88404.
- Zeng BY, Iravani MM, Jackson MJ, Rose S, Parent A, and Jenner P (2010) Morphological changes in serotonergic neurites in the striatum and globus pallidus in levodopa primed MPTP treated common marmosets with dyskinesia. *Neurobiol Dis* **40**:599–607.
- Zhang D, Bordia T, McGregor M, McIntosh JM, Decker MW, and Quik M (2014) ABT-089 and ABT-894 reduce levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Mov Disord* **29**:508–517.
- Zhang D, Mallela A, Sohn D, Carroll FI, Bencherif M, Letchworth S, and Quik M (2013) Nicotinic receptor agonists reduce L-DOPA-induced dyskinesias in a monkey model of Parkinson's disease. *J Pharmacol Exp Ther* **347**:225–234.
- Zhang D, McGregor M, Bordia T, Perez XA, McIntosh JM, Decker MW, and Quik M (2015) $\alpha 7$ nicotinic receptor agonists reduce levodopa-induced dyskinesias with severe nigrostriatal damage. *Mov Disord* **30**:1901–1911.
- Zubair M, Jackson MJ, Tayarani-Binazir K, Stockwell KA, Smith LA, Rose S, Olanow W, and Jenner P (2007) The administration of entacapone prevents L-dopa-induced dyskinesia when added to dopamine agonist therapy in MPTP-treated primates. *Exp Neurol* **208**:177–184.

Address correspondence to: Philippe Huot, Montreal Neurological Institute, 3801 University St, BT 209, Montreal, QC, Canada H3A 2B4. E-mail: philippe.huot@mcgill.ca
