Minireviews

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

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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; Beshpalov 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

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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	Bézard 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	Bézard 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)
Rauwolscine [<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.

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