Neuropharmacology xxx (2018) xxx-xxx

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com

Invited review

Repurposing drugs to treat L-DOPA-induced dyskinesia in Parkinson's disease

Tom H. Johnston[a, b, *], Alix M.B. Lacoste[c, 1], Naomi P. Visanji[d, 1], Anthony E. Lang[d], Susan H. Fox[d], Jonathan M. Brotchie[a, b]

[a] Krembil Research Institute, University Health Network, Toronto, ON, Canada
[b] Atuka Inc., Toronto, ON, Canada
[c] IBM Watson Health, New York, NY, USA
[d] Edmund J Safra Movement Disorders Clinic, Division of Neurology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 5 April 2018
Received in revised form 29 May 2018
Accepted 31 May 2018
Available online xxx

ABSTRACT

In this review, we discuss the opportunity for repurposing drugs for use in L-DOPA-induced dyskinesia (LID) in Parkinson's disease. LID is a particularly suitable indication for drug repurposing given its pharmacological diversity, translatability of animal-models, availability of Phase II proof-of-concept (PoC) methodologies and the indication-specific regulatory environment. A compound fit for repurposing is defined as one with appropriate human safety-data as well as animal safety, toxicology and pharmacokinetic data as found in an Investigational New Drug (IND) package for another indication. We first focus on how such repurposing candidates can be identified and then discuss development strategies that might progress such a candidate towards a Phase II clinical PoC. We discuss traditional means for identifying repurposing candidates and contrast these with newer approaches, especially focussing on the use of computational and artificial intelligence (AI) platforms. We discuss strategies that can be categorised broadly as: *in vivo* phenotypic screening in a hypothesis-free manner; *in vivo* phenotypic screening based on analogy to a related disorder; hypothesis-driven evaluation of candidates *in vivo* and *in silico* screening with a hypothesis-agnostic component to the selection. To highlight the power of AI approaches, we describe a case study using IBM Watson where a training set of compounds, with demonstrated ability to reduce LID, were employed to identify novel repurposing candidates. Using the approaches discussed, many diverse candidates for repurposing in LID, originally envisaged for other indications, will be described that have already been evaluated for efficacy in non-human primate models of LID and/or clinically.

1. Introduction

The majority of individuals with Parkinson's disease (PD) treated with dopamine-replacement therapy eventually develop abnormal involuntary movements, L-DOPA-induced dyskinesia (LID) (Hely et al., 2005). LID can be debilitating and lacks treatment options, with only one drug, amantadine, in two formulations, available for this indication, only one approved, one used off-label (Fox et al., 2011). LID therefore represents a significant unmet therapeutic need. Repurposing molecules with proven safety in humans, at Phase II or beyond, can be an extremely efficient method to rapidly bring new treatments to patients. Repurposing bypasses many high-risk phases of the drug development process. Repurposing, entering development for a new indication at Phase IIa, is significantly less costly, takes as little as 4 years (Braun et al., 2010) and has a ~3000 times greater chance of reaching patients than a novel drug (Hub, 2015; Medicine, 2014). In this review, we focus on features of LID that make it a particularly attractive candidate for drug repurposing, discuss historical and new approaches to identifying potential drugs that can be repurposed for LID, identify mechanisms to prioritise testing of new compounds and discuss challenges especially in translation from preclinical testing to Phase II clinical proof-of-concept (PoC) trials.

PD is the second most common neurodegenerative disease of aging, the cause of which remains largely unknown (Kalia and Lang, 2015). There is currently no treatment able to slow down or prevent the progressive degeneration of dopaminergic cells in the substantia nigra that underlies the characteristic motor symptoms of bradykinesia, akinesia and rigidity (Kalia and Lang, 2015). The cornerstone of therapy remains dopamine-replacement, most commonly with L-3,4-dihydroxyphenylalanine (L-DOPA) (Kalia and Lang, 2015), which can provide important symptomatic relief for some time. However, this treatment is fraught with complications, most notably the development of LID. As the disease progresses, the majority of patients will experience some degree of LID in response to dopamine replacement therapy, thus by 15 years after diagnosis, greater than 90% of PD patients have developed LID (Hely et al., 2005). LID, particularly when severe, is associated with a wide range of significant co-morbidities including interference with vital daily activities including eat-

* Corresponding author. Krembil Research Institute, 60 Leonard Avenue, 8KD-402, Toronto, ON, M5T 2R1. Canada.
Email address: tom.johnston@uhnresearch.ca (T.H. Johnston)
[1] Authors contributed equally.

https://doi.org/10.1016/j.neuropharm.2018.05.035
0028-3908/

ing and drinking (Bachmann and Trenkwalder, 2006), increased levels of anxiety, depression, psychosocial issues and stigma (Daneault et al., 2013), and an increased risk of falls, which leads to increased nursing home placement and poor overall survival (Ashburn et al., 2001; Rudzinska et al., 2013). A 2014 Priority Setting Partnership identified LID third among 96 unmet needs in PD (Deane et al., 2014).

An estimated 7–10 million people are currently living with PD worldwide, with an additional 75,000 individuals newly-diagnosed each year in North America alone. With no disease-modifying therapy and an increasingly aged population, the socio-economic burden of LID is only set to increase over coming years. To date, despite many costly trials evaluating novel drugs, there are few oral agents that are clinically useful. Only one is widely used, immediate release amantadine, the non-selective NMDA receptor antagonist, used off-label. A novel, extended release formulation of amantadine was approved in 2017 by the FDA (currently for use in the USA alone and branded as GOCOVRI), for the treatment of LID. In the context of LID, and this review, amantadine is itself a repurposed drug. Initially used as a prophylactic treatment for influenza (Davies et al., 1964), in 1969, Schwab and colleagues noted an anti-parkinsonian effect of the drug in a single patient (Schwab et al., 1969). Several subsequent clinical trials demonstrated a significant anti-parkinsonian benefit of amantadine leading to its use as a symptomatic therapy for PD, often in combination with L-DOPA (Parkes et al., 1971a, 1971b), with an approval for treatment of PD, though not LID. It was not until nearly 30 years later, that anti-dyskinetic actions of NMDA antagonists were reported in animal models of PD, including the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned non-human primate (NHP) ((Blanchet et al., 1998)). These findings led to re-evaluation of the effects of amantadine in PD and, in 1998, two independent groups reported a reduction in LID in patients taking amantadine and advocated for the use of the drug as an anti-dyskinetic agent (Rajput et al., 1998; Verhagen Metman et al., 1998c). The off-label use of immediate release amantadine has been shown to provide significant relief of LID in up to a third of patients (Fox et al., 2011). In some individuals, long-term amantadine, at least, to date, in the immediate release form may be compromised by tachyphylaxis, which has been reported over a period of time as short as 6 months (Thomas et al., 2004), although many patients do retain clinical benefit for long periods of use. Furthermore, amantadine is often poorly tolerated due to cognitive problems, confusion, hallucinations and ankle oedema and is not appropriate for individuals with renal failure. The relative better tolerability of the extended release amantadine is suggested by the once-daily dosing at night but long-term clinical use is yet to confirm this proposition.

Thus, LID remains a largely unmet need and represents a particularly opportune candidate for drug repurposing for several reasons which can be broadly categorised as,

- diversity of pharmacology,
- translatability of animal models,
- availability of powerful Phase II proof-of-concept methodologies, and,
- regulatory environment.

The multifaceted pathophysiology of LID is relatively well-understood, incorporating both dopaminergic and non-dopaminergic systems, including adenosine, adrenergic, cannabinoid, cholinergic, γ-aminobutyric acid (GABA)-ergic, glutamatergic, histaminergic, opioid, and serotonergic systems (Huot et al., 2013). This diverse and complex pathophysiology may in part underlie the difficulty in developing treatments with strong and broadly applicable efficacy. However, on the other hand, this diverse array of mechanisms offers a multitude of potential therapeutic targets that can potentially be capitalized upon using a targeted repurposing strategy. It is also a possibility that selectivity for one of these targets in a repurposed drug may not be a prerequisite and may even be desirable.

There are excellent pre-clinical models for LID in both rodents and NHP, allowing for reliable testing of efficacy of potential drugs for repurposing for LID. Critically, in both rodent and non-human primate models of LID, the effect of test compounds on parkinsonian symptoms can be assessed concurrently in the same animals to ensure that compounds that reduce LID do so without reducing the anti-parkinsonian benefits of L-DOPA, providing crucial support for continued development. In rats or mice bearing a unilateral 6-OHDA-induced lesion of the nigrostriatal tract, repeated administration of L-DOPA induces a dyskinesia-like phenotype; abnormal involuntary movements (AIMs) including rotational asymmetry (Lundblad et al., 2002). This model has a good track record across multiple independent laboratories, for several classes of drug target, of predicting anti-dyskinetic efficacy in higher species such as the NHP (Lundblad et al., 2002; Monville et al., 2005). In NHPs rendered parkinsonian with MPTP, repeated administration of L-DOPA induces a phenotype that is remarkably close to LID exhibited in PD patients (Bedard et al., 1986; Clarke et al., 1987), allowing for assessment of parkinsonism and dyskinesia using scales equivalent to those used in the clinic (Fox et al., 2012). Thus, the dyskinetic MPTP primate has excellent face validity for treating dyskinesia and has been instrumental in the development of several approaches for treating motor complications in PD. Across a range of targets and many compounds, the MPTP-lesioned NHP has consistently predicted the efficacy of compounds in reducing LID in Phase II proof-of-concept studies (Fox et al., 2006), where those clinical studies were designed,

- in a randomized, double blind, controlled manner, with appropriate power
- to ensure the same levels of drug exposure/target engagement were achieved in both species, and,
- where efforts were made to evaluate the same, or functionally-equivalent, measures of LID and parkinsonism in both species

The third aspect of LID research that renders it especially amenable to repurposing is that validation in Phase II PoC trials can be completed in a relatively rapid manner. Thus, in contrast to the extremely challenging trials for disease-modifying therapies, demonstration of anti-dyskinetic efficacy can be accomplished in a compact time frame of weeks to months, with small numbers of patients. For instance, an intravenous L-DOPA clinical trial protocol to study novel anti-dyskinetic compounds can be usefully employed using just two 2-week double-blind crossover treatment periods, with an intervening 2-week washout. In such a design, involving only 13 patients, we have recently demonstrated a clinical benefit of repurposing dextromethorphan/quinidine for LID (Fox et al., 2017).

Finally, the regulatory environment, at least in the US, is receptive to developing treatments for LID. In the US, the Orphan Drug Act grants special status to a drug to treat rare diseases that affect fewer than 200,000 people in the United States, and thereby reduces financial, legal and intellectual property disincentives to drug repurposing (Meekings et al., 2012). Adamas Pharmaceuticals, were recently successful in their bid to have the above-discussed extended release version of amantadine granted orphan drug designation for the treatment of LID. Similarly, with Juvantia's initial development of the alpha-adrenergic antagonist, fipamezole, there is precedent for FDA providing Fast Track Designation for LID treatments, to facilitate the development path.

In concert, these features make repurposing an existing drug for a new indication of LID a very attractive prospect. Potential drugs can be selected for repurposing based on a good understanding of mechanism of action, can be screened in reliable pre-clinical models of the disease and rapidly validated in relatively short Phase II clinical trials in PD patients. Finally, due to orphan status, there is an economic incentive to repurpose off-patent drugs or develop drugs for which there is significant clinical experience but have, perhaps, failed to show efficacy in another indication.

2. How do we identify new candidate drugs for use in LID?

The clear benefits of drug repurposing and features that render LID particularly amenable to a repurposing strategy highlight the need to optimise the way in which we identify candidates, from the vast number of regulatory approved compounds, and prioritise for development.

For the purpose of this review, we define a compound fit for repurposing as a compound for which there is good human safety data, as well as animal safety and toxicology and pharmacokinetic data as would be found in an Investigational New Drug (IND) package in place for another indication. Thus, the compounds of interest herein may or may not have received regulatory approval for any indication. We take this view as not only are there many approved molecules on the market that can be repurposed but because there are many more, likely safe, and potentially-useful molecules that may have failed during development for efficacy reasons and we want to be able to capture any potential value for LID in those.

The goal of this review is not only upon how to identify repurposing candidates but also on defining a repurposing pathway towards a deliverable of Phase II clinical PoC. We do not discuss in any detail where a program might go beyond such clinical PoC. This is not to diminish the importance, or complexity, of Phase III development but depending on the nature of the compound and its clinical history that path to widespread clinical use in LID could be very different. Indeed, after PoC a repurposed compound might not even require Phase III studies, as was, for instance, the case with generic, immediate release amantadine in LID.

Several of the successfully repurposed drugs outside of LID have relied upon serendipity. For example, an angina medication developed in 1989, sildenafil, had a notable side effect leading to it now being marketed to treat erectile dysfunction (Ban, 2006) and, indeed, the original indication of amantadine in PD was not to address LID. However, it is clearly incumbent upon the pharmaceutical development community to be more proactive and actively seek candidates. In more recent times, the ever increasing cost of drug development has led to a surge of interest in repurposing, driving research into more effective methodologies to identify drugs that can be repurposed for new indications including those capitalising on big-data analytics, computational modelling and high-throughput screening (Nosengo, 2016). In the next section of this review, we discuss traditional drug development strategies and contrast these with newer approaches, focussing on the use of artificial intelligence platforms, to identifying suitable drugs for repurposing for LID.

We discuss several approaches to the identification of novel therapies for LID. These can be categorised broadly as either:

- *in vivo* phenotypic screening in a relatively hypothesis-free manner
- *in vivo* phenotypic screening based upon analogy to a related disorder
- hypothesis-driven evaluation of candidates *in vivo*
- *in silico* screening by computational methods and AI with a hypothesis-agnostic component to the selection

In this review, we will briefly overview the first three of these and emphasize the fourth that we propose is a major area of innovation and a significant step in the evolution of drug discovery for LID. Table 1 lists a range of diverse examples of drugs across many different classes of compound that have been examined as repurposing candidates for LID.

2.1. Phenotypic screening

Perhaps the most influential paper in drug-repurposing in LID was published more than 25 years ago by Gomez-Mancilla et al. (Gomez-Mancilla and Bedard, 1993). These authors, in a relatively hypothesis-free manner, evaluated a range of compounds, with various targets, for anti-LID efficacy in the MPTP-lesioned NHP. The power of the approach came from the power of the animal model, not only to demonstrate a reduction in LID but to be able to do so without diminishing anti-parkinsonian benefit. This one paper alone validated new drug targets for LID and while the compounds used within that study may not themselves have been further developed, the work catalysed the repurposing of several drugs for LID. Some of these, e.g. idazoxan, targeting alpha-2 adrenergic receptors (Rascol et al., 2001), clozapine (Durif et al., 2004) and quetiapine (Katzenschlager et al., 2004), targeting 5-HT2A, and likely other 5-HT, receptors, were subsequently shown to have efficacy to reduce LID in Phase II PoC studies (Fox et al., 2006).

An alternative approach is to look towards diseases with a similar phenotype to LID and likely overlapping neural mechanisms to identify repurposing opportunities. A recent example of this is the identification of pridopidine (TV-7820, formerly ACR16 and ASP2314) as a potential repurposing candidate for LID. Pridopidine has been in development for the treatment of abnormal movements in Huntington's disease, with three clinical trials recently completed, MermaiHD and HART and PRIDE-HD (de Yebenes et al., 2011; Huntington Study Group, 2013; Kieburtz et al., 2017). Recently, in a move based upon analogy rather than a mechanistic understanding, as the mechanism of action of pridopidine in HD is unclear, in the MPTP-lesioned NHP, pridopidine has been shown to reduce LID without compromising anti-parkinsonian benefit of L-DOPA (Johnston et al., 2017). These findings suggest that pridopidine could be repurposed for LID and clinical trials could be initiated immediately.

2.2. Hypothesis-driven evaluation

A useful approach that, historically, has driven the identification and evaluation of repurposed compounds for LID is that supported by advances in our understanding of the neuropharmacological mechanisms responsible for the development and expression of the symptoms of LID. The best example of this, amantadine, emerged from the understanding of the role of aberrant NMDA transmission in the corticostriatal pathway, and how it might be responsible for overactivity of the “direct” striatal output pathway (DeLong, 1990). This led to the evaluation of a range of NMDA antagonists as anti-dyskinetic therapies, in both rodent and NHP models of LID ((Papa et al., 1995; Papa and Chase, 1996)). The success of these led directly to the hypothesis that amantadine might be effective for LID, in addition to its previously-recognised, if somewhat modest, against the core parkinsonian motor problems. Amantadine was a particularly attractive agent for repurposing as it was generic, already in use in PD patients, and thus clinical PoC at Phase II and marketing was sufficient to drive its widespread off-label use.

Repurposing efforts for LID have also focused on the histaminergic system. H2 receptors are highly expressed within basal ganglia,

Table 1

Transmitter system targeted	Target	Compound	Prior indication	PoP for LID in rodent	PoP for LID in NHP	Clinical PoC in LID	Comments
Glutamate	NMDA	Amantadine	Anti-viral (Davies et al., 1964)/Parkinsonism (Schwab et al., 1969)	Yes (Dekundy et al., 2007; Lundblad et al., 2002)	Yes (Blanchet et al., 1998)	Yes (Rajput et al., 1998; Verhagen Metman et al., 1998c)	Widely used in clinical practice
		Memantine	Alzheimer's disease (Fleischhacker et al., 1986)	Yes (Tronci et al., 2014)	N/A	Yes (Varanese et al., 2010; Vidal et al., 2013)	Data gathered so far suggest that memantine may be a useful anti-dyskinetic drug but primate and further clinical studies are warranted
		Dextromethorphan/ Quinidine	Anti-tussive (Boyd, 1946)/arrhythmia (Drury and Iliescu, 1921)	* Yes (Jimenez et al., 1999; Marin et al., 2000)	No	Yes (Fox et al., 2017; Verhagen Metman et al., 1998a, 1998b)	* PoP for motor complications generally but not LID specifically. Successful at Phase II, continues development
	AMPA	Topiramate	Epilepsy (Harden, 1994)	Yes (Kobylecki et al., 2011)	Yes (Silverdale et al., 2005)	No (Kobylecki et al., 2014)	Poorly tolerated and worsened LID in PD patients
	Glutamate release	Naftazone	Haemostasis (Charles and Coolsaet, 1972)	N/A	Yes (Brotchie et al., 2007)	Yes (Rascol et al., 2012)	Development discontinued despite positive pilot data at Phase II
	mGlu5	Fenobam	Anxiety (Pecknold et al., 1982)	Yes (Rylander et al., 2010)	Yes (Rylander et al., 2010)	N/A	–
Opioid	OR	Naloxone	Opioid overdose (Fink et al., 1968)	Yes (Carey, 1991; Lundblad et al., 2002)	Inconclusive (Gomez-Mancilla and Bedard, 1993; Klintenberg et al., 2002; Samadi et al., 2003)	No (Fox et al., 2004)	NHP data were inconclusive, one group finding a decrease, the other an exacerbation and a third no effect on LID. Effect on AIMs in rat model is modest
		Naltrexone	Alcohol abuse (Meyer et al., 1975)	N/A	Inconclusive (Henry et al., 2001; Samadi et al., 2003)	No (Rascol et al., 1994)	NHP data were inconclusive, one group finding a decrease, the other an exacerbation
	MOR/KOR	Nalbuphine	Analgesia (Elliott et al., 1970)	N/A	Y (Potts et al., 2015)	N/A	–
Serotonin	5-HT2A	Quetiapine	Schizophrenia (Wetzel et al., 1995), bipolar disorder (Ghaemi and Katzow, 1999)	N/A	Yes (Oh et al., 2002)	No (Katzenschlager et al., 2004)	Doses higher than 25 mg may be needed to provide clinical PoC
		Clozapine	Schizophrenia (Matz et al., 1974)	Yes (Lundblad et al., 2002)	Yes (Grondin et al., 1999)	Yes (Durif et al., 1997, 2004; Pierelli et al., 1998)	A useful and widely-accepted alternative to amantadine in clinical practice (Fox et al., 2018)
	5-HT1A/B	Eltoprazine	Aggression (Verhoeven et al., 1992)	Yes (Ghiglieri et al., 2016; Pinna et al., 2016; Tronci et al., 2015)	Yes (Bezard et al., 2013; Ko et al., 2017)	Yes (Svenningsson et al., 2015)	While rodent data are very strong, NHP data suggest that the clear anti-LID effects may prove hard to differentiate from loss of anti-parkinsonian benefit
Histamine	H2	Famotidine	Peptic acidosis (Smith, 1985)	Yes (Lim et al., 2015)	Yes (Johnston et al., 2010d)	No (Mestre et al., 2014)	Appears to be well-tolerated in PD patients (Molinari et al., 1995)
	H3	Immepip	Migraine, ischemic arrhythmias (Wijtmans et al., 2007)	No (Papathanou et al., 2014)	Yes (Gomez-Ramirez et al., 2006)	N/A	–
Dopamine	D2	Pridopidine	Huntington disease (Lundin et al., 2010)	N/A	Yes (Johnston et al., 2017)	N/A	Other potential MoAs including sigma 1, alpha 2 adrenergic and 5-HT1A receptors
	D4	L-745,870	Schizophrenia (Bristow et al., 1997)	N/A	Yes (Huot et al., 2012b)	N/A	–
Noradrenaline	Alpha2	Idazoxan	Depression (Grossman et al., 1999)	Yes (Barnum et al., 2012; Johnston et al., 2005; Wang et al., 2014)	Yes (Fox et al., 2001; Grondin et al., 2000; Henry et al., 1999)	Yes (Rascol et al., 2001)	While clinical PoC was efficacy was shown at a dose of 20 mg another study did not confirm this (Manson et al., 2000)

Acetylcholine	nAChRs	Nicotine	Smoking cessation (West et al., 1984)	Yes (Bordia et al., 2008; Huang et al., 2011; Quik et al., 2013a)	Yes (Quik et al., 2013b; Zhang et al., 2015)	N/A	–
Other	SV2A	Levetiracetam	Epilepsy (Betts et al., 2000)	Yes (Du et al., 2015)	Yes (Bezard et al., 2004; Hill et al., 2003)	Yes (Stathis et al., 2011; Wolz et al., 2010)	Clinical PoC was provided by two studies, however, magnitude of efficacy was modest and another study did not confirm this (Wong et al., 2011)
	oestrogen	Tamoxifen	Cancer (Ward, 1973)	N/A	Yes (Smith et al., 2007)	N/A	–

particularly on the GABAergic striatopallidal and striatonigral pathways (Anichtchik et al., 2001; Vizuete et al., 1997) and it was subsequently shown that an H2 antagonist, famotidine (Schunack, 1989), already in clinical use for treatment of peptic ulcer and gastroesophageal reflux, was efficacious at reducing LID in the MPTP-lesioned macaque (Johnston et al., 2010d). In this instance however, translation to the clinic, following a small PoC trial, was not successful (Mestre et al., 2014).

There has been a long history of exploring the role of the opioid system in LID (Fox et al., 2006). Following chronic L-DOPA therapy and the expression of dyskinesia, levels of opioid peptides and the mRNA encoding their precursors are elevated in animal models of parkinsonism (Cenci et al., 1998; Engber et al., 1991) and in post-mortem studies from patients with PD with motor fluctuations after long-term levodopa use, there is increased striatal preproenkephalin (PPE)-B (Henry et al., 2003) and PPE-A (Calon et al., 2002; Nisbet et al., 1995), expression. These findings let to the hypothesis that increased opioid neuropeptide neurotransmission accompanies and thus may be involved in the pathophysiology of dyskinesia and that reducing activity of the opioidergic system may be of benefit. A range of studies latterly explored the potential for non-selective opioid antagonists such as naloxone and naltrexone that were already in clinical use primarily for the management of alcohol and opioid dependence (Budd, 1987). Studies in the MPTP-lesioned primate with LID produced conflicting results. The non–subtype-selective opioid receptor antagonists, naloxone and naltrexone, either have no effect (Gomez-Mancilla and Bedard, 1993), can significantly reduce dyskinesia (Henry et al., 2001; Klintenberg et al., 2002) or can exacerbate LID (Samadi et al., 2003). This discrepancy has led to conflicting concepts that opioids represent either a compensatory/protective mechanism or are a cause of dyskinesia. In double-blind randomized placebo-controlled phase IIa clinical trials, low-dose oral naltrexone (approximately 1 mg/kg) failed to show any effect (Rascol et al., 1994), whereas high-dose naltrexone (5 mg/kg) had a minimal effect (Manson et al., 2001). Neither exacerbated dyskinesia nor affected parkinsonian disability. A trial using IV infusion of 0.3 μg/kg/min naloxone, a dose known to block central opioid receptors, also failed to demonstrate any reduction in dyskinesia, but did show an extension in the duration of action of L-DOPA (Fox et al., 2004).

Dopamine D_4 receptor antagonism garnered considerable attention as target for LID based upon studies performed with the purported 5-HT_{1A} agonist sarizotan. Sarizotan reduces dyskinesia, or its equivalent, in rodent and primate models (Bibbiani et al., 2001; Gregoire et al., 2009; Marin et al., 2009) and, indeed, was taken into clinical development for this indication. Sarizotan was found to reduce LID in three Phase II clinical trials (Bara-Jimenez et al., 2005; Goetz et al., 2007; Olanow et al., 2004). However, it failed to advance beyond two large scale Phase III studies, which showed no greater benefit than placebo (Goetz et al., 2008; Muller et al., 2006; Rascol et al., 2006). Of concern, sarizotan also acts as a D_2 antagonist, likely resulting in the exacerbation of PD symptoms. While, the anti-dyskinetic efficacy of sarizotan is generally attributed to an action at 5-HT_{1A} receptors it is essentially equipotent at D_4 receptors, where it acts as an antagonist (Bartoszyk et al., 2004; Kuzhikandathil and Bartoszyk, 2006). Thus, the anti-dyskinetic properties of sarizotan, seen at Phase II, may have been just as likely produced by D_4 receptor antagonist actions. To test this hypothesis and validate the D_4 receptor as a target for LID, a study was conducted to assess the ability of a far more D_4-selective ligand, L-745,870, which, in contrast to both sarizotan and clozapine, is a highly potent and selective dopamine D_4 receptor antagonist, with affinity in the picomolar range (Ki, 0.43 nM). In the 1990's, L-745,870 was developed by Merck & Co. Inc. for an indication of psychosis in schizophrenia and entered Phase II studies. The compound had thus already undergone extensive pre-clinical testing and possessed a wealth of safety and tolerability data in humans, though none in PD. The development of L-745,870 was terminated as it did not show efficacy against psychosis (Bristow et al., 1997; Kramer et al., 1997). Although unsuccessful in the context of psychosis, as a repurposed compound L-745,870 may have promise in LID since it has already demonstrated efficacy in the MPTP-lesioned macaque (Huot et al., 2012a).

Another example of identification of a potential repurposing candidate came, in the mid-1990s, from an increasing understanding of the role of the CB1 cannabinoid receptor in the regulation of basal ganglia transmission (Felder et al., 1996; Rodriguez de Fonseca et al., 1998). Indeed, the CB1 agonist nabilone, a drug approved for the treatment of chemotherapy-associated nausea, was shown to reduce LID in the MPTP-lesioned NHP (Fox et al., 2002). Subsequently, in a Phase II PoC study, in nine patients, these effects were confirmed clinically (Sieradzan et al., 2001). However, for non-efficacy issues these findings have not lead to nabilone having widespread use in LID. In a similar way, advances in understanding of synaptic physiology led to identification of SV2A as a target for LID. SV2A is a vesicular protein integral to synaptic release and vesicle re-cycling (Bajjalieh et al., 1993), and it was hypothesized that targeting it would change firing patterns, and reduce LID, in a manner already validated, more invasively, by deep-brain stimulation (Dostrovsky et al., 2000). This hypothesis led to the identification of the anti-convulsant levetiracetam as a repurposing candidate. Indeed, levetiracetam engages SV2A and has excellent anti-dyskinetic efficacy in the MPTP-NHP (Bezard et al., 2004). However, these benefits could not be translated to efficacy at Phase II as the compound was poorly tolerated in the PD patient population (Stathis et al., 2010; Wolz et al., 2010). These last two examples, nabilone and levetiracetam, highlight the importance not only of efficacy but also tolerability in repurposing. PD patients are typically aged and may have several other therapies to combine with the new drug, and tolerability is not always as good as in other populations.

2.3. The potential of computational approaches

In recent years, we have seen increasing application of computational drug discovery strategies and LID has been a focus of several of these. In addition to the attractiveness of LID as an indication for which to be repurposed, as discussed above, a further consideration, relevant specifically to computational approaches is that, with approximately 1600 MedLine abstracts that mention LID, or one of its component phenomenologies, the body of literature around LID is now at the "big data" stage. Thus, with these types of dataset, meaningful insights can be gleaned by AI approaches. At the same time, the computational technologies to support drug re-purposing have matured. There has been a recent explosion in the number of articles detailing methods for computational drug repositioning. Of the ~500 articles retrieved from the search "computational drug repositioning" in PubMed, ~100 of them were published in 2017. These advances have also driven the formation of several companies that use computational methods to define novel therapeutic approaches, a major focus being repurpose-able drugs, e.g. BenevolentAI, IBM Watson, Exscientia, GNS Healthcare and Insilico Medicine. These companies can work as standalone drug discovery entities or in partnership with more traditional pharmaceutical companies e.g. both GSK and Sanofi with Exscientia and Genentech with GNS.

Not surprisingly, given the recency of these advances, at the time of writing, to our knowledge, no drug has successfully reached the clinic as a repurposed drug based on computational methods. However, the increase in the number of pharmaceutical companies embracing AI, and the availability of a range of platforms (both software and web-based) increases the chances of a computationally-identified drug reaching the clinic in the near future. In Section 3, we will now move on to discuss in detail, how these might be implemented to provide novel repurposing candidates for LID. As will be discussed in Section 4, validating predicted compounds in animal models *in vivo* will be critical to advancing these possible therapies, highlighting the necessity for quality platforms for testing efficacy as well as clinical methodologies, Section 5.

3. The promise of computational drug repurposing strategies

There are several ways to classify computational drug repurposing methodologies for LID. For the purposes of this review, we will define five approaches,

- drug to target predictions,
- target to disease predictions,
- drug similarity approaches,
- disease similarity approaches, and,
- drug to disease predictions.

For LID, as with other diseases, the choice of the most appropriate method is limited by the type, quality and depth of information found in the literature and in public databases as well as nuances of each methodology. For example drug repurposing for LID is not applicable to methods using electronic medical record data (e.g. (Kuang et al., 2016)) as these methods rely on International Classification of Disease (ICD) codes rendering LID unsearchable.

3.1. Drug to target predictions

Computational approaches have been assisting with drug to target predictions for many years. Structure-based techniques such as molecular docking, for example, rely on modelling the three-dimensional physical interaction between compounds and protein targets. A recent example, using molecular docking and binding energy evaluated 150 drugs for Alzheimer's disease and proposed several antipsychotic drugs for five major protein targets (AChE, BuChE, BACE1, MAO and NMDA) in Alzheimer's disease (Kumar et al., 2017). The drug benperidol was found to have a higher docking score for AChE compared to the positive control donepezil, and also bound to the four other major Alzheimer's targets. In this case, computational techniques enabled the rapid identification of an already-approved drug that targets multiple pathways of a disease pathophysiology, offering a higher therapeutic potential compared to the traditional one drug one target approach. Ligand-based chemical-protein predictions include Quantitative structure-activity relationship (QSAR) modelling, which has also been applied in polypharmacology towards identifying compounds for multiple targets in Alzheimer's disease (Fang et al., 2017).

3.2. Target to disease predictions

Many diverse tools are presently being developed for target to disease predictions. The concept is that if relevant targets for a disease are known, then existing drugs for these targets are good candidates. A limiting factor in applying this approach is how much is known and how much remains to be discovered in terms of targets and pathways in LID. Furthermore, for conditions with multiple disrupted pathways, as is believed to be the case in LID (Huot et al., 2012c), this methodology is less attractive due to the complexity of the problem. Variations of network-based approaches to infer novel target to disease associations are increasingly common. A notable method that strives to go beyond individual protein predictions to identify protein modules involved in diseases leverages networks of protein-protein interaction and disease similarity metrics (Vanunu et al., 2010). In the era of precision medicine, another approach to identifying disease targets is to correlate gene expression profiles or other omics data with disease progression in individuals or sub-groups of patients (see for example (Bertrand et al., 2015)).

3.3. Drug similarity methods

This methodology relies on the simple concept that drugs similar to those already efficacious for a particular disease may be applicable to the same disease. One of the oldest drug similarity methods are chemical structure similarity-based approaches. The rationale is that a similar chemical structure likely leads to a similar biological outcome. However, small changes to a chemical's structure, especially in the ligand binding site, can have vast consequences for the binding of primary targets, for off-target effects and ultimately for efficacy. With respect to LID the only drug approved for the treatment of LID is amantadine, however, as discussed above, amantadine has many side effects and also suffers from tachyphylaxis. Therefore, drug similarity methods could be applied to identify other drugs with a similar chemical structure to amantadine in the hope that they may remain efficacious but exhibit a more favourable side effect profile.

Similarity of drug effects can also be assessed using transcriptional responses, for example by comparing gene expression profiles following different drug treatments (Iorio et al., 2010). More recent approaches combine several drug similarity measures in comprehensive models. For example, Zhang and colleagues created a framework that integrates chemical, biological and phenotypic data on drugs sources (Zhang et al., 2013). The limitation of this approach is in the availability of the data on existing drugs used to treat a specific condition. In LID, as will be discussed in a later section, there are several drugs that have shown efficacy in animal models or early clinical tri-

als, that could form the basis for such predictions. An approach that overcomes the limitation in availability of database information is to leverage large-scale publication data to infer drug similarity. For example, IBM Watson mines millions of scientific publications and patents to draw parallels between concepts such as drugs and targets (Nagarajan et al., 2015; Spangler et al., 2014). The application of this method in LID will be discussed in the case study section below.

3.4. Disease similarity methods

This method relies on the notion that similar diseases can be treated by the same drug(s). Methods relying on disease similarity are in principle parallel to ones relying on drug similarity. Many of the same features can be exploited, including disease phenotypes, transcriptional profile, network-based approaches, etc. More recent approaches leverage several types of data sources to infer similarity. For example, one method uses an analysis of disease-related mRNA expression data with a protein interaction network to define disease similarity, leading to the identification of common drugs and drug targets (Suthram et al., 2010). The challenge of these methods for LID is the limited availability of structured data available for this condition, such as in widely-used databases like OMIM (Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), 2017. World Wide Web URL: https://omim.org/), or MalaCards (http://www.malacards.org).

3.5. Drug to disease predictions and integrative approaches

There are a variety of direct drug repurposing methods. Many of these techniques integrate different data sources for predictions. One method leverages the wealth of publicly-available gene expression data. By examining the sets of genes that are up- and down-regulated in a disease state compared to a normal state, it is possible to create a gene expression profile, or signature, of a disease. Similarly, drug signatures can be acquired by analyzing how drugs affect gene expression. If a gene is differentially regulated in a disease state, returning the protein it codes for to normal levels may be an effective treatment. Hence, diseases with opposite expression signatures to a particular drug may constitute possible new indications for this drug (Sirota et al., 2011). The same principle could be applied to other types of omics data if available for both drugs and conditions. Due to technical advances, the availability of public omics databases is growing at a remarkable speed. Large repositories such as the Gene Expression Omnibus (Barrett et al., 2012) that collects microarray and sequencing data across many publications are a source for gene expression changes in a range of diseases. Gene expression databases for drugs include C-map (Subramanian et al., 2017) and DrugSig (Wu et al., 2017). One of the first studies to use gene expression data for computational drug repurposing identified the potential utility of the anticonvulsant drug topiramate for inflammatory bowel disease (Dudley et al., 2011). Although topiramate showed promise in a preclinical rodent colitis model, a pharmacoepidemiology retrospective cohort study using claims data found no evidence of a therapeutic benefit of topiramate in patients with inflammatory bowel disease (Crockett et al., 2014). There are limitations to using gene expression data alone: gene, protein and metabolite expression measurements can be quite noisy and incomplete, and the level of granularity in terms of cell or tissue type is often restricted. In addition, a major limitation is that if transcriptional disease data is not available, this approach cannot be used. At the time of writing, we found 4 datasets submitted to the gene expression omnibus (Barrett et al., 2012) regarding LID, however all are from rodents, none are human. An additional limitation of this approach for LID is that treatment for LID should not impede on L-DOPA's antiparkinsonian effects, and it can be difficult to determine which gene expression changes are related to benefits for symptoms of PD versus leading to LID. Therefore, at present, the use of gene expression or omics data in drug repurposing in LID is of limited applicability.

Other direct drug repurposing approaches integrate components of methodologies discussed in previous sections. For example, Zhang et al. (2014), created matrices of disease and drug similarity measures and used an optimization model to propose novel drug indications. An additional advantage of this prediction model is that it can determine the relevance of different information sources on drugs and diseases for individual predictions (Zhang et al., 2014). Another recent model worth noting uses network analysis to propose drug-disease associations based on a variety of features and data (Huang et al., 2013).

3.6. Existing web-based tools for repurposing

We will discuss a sample of the most recent platforms available for drug repurposing, illustrating the diversity of computational approaches discussed above. Two platforms, Open Targets and Project Rephetio combine different data sources and are available in the browser. However, due to the limited availability of information about LID in traditional databases, our case study below makes use of a literature mining approach using an IBM Watson engine.

Open Targets was created in 2015 out of a collaboration between multiple institutions and pharmaceutical companies. The platform combines several data sources such as genetic associations, mutation information, drug, biological pathways, and text mining. While the browser application (www.targetvalidation.org/) currently only allows users to identify known and predicted disease-target associations, a recent article demonstrated its utility in drug repurposing (Khaladkar et al., 2017). The computational workflow described in the study uncovered thousands of potential new indications for hundreds of existing drug targets. Disease names come from the Experimental Factor Ontology (www.ebi.ac.uk/ols/ontologies/efo), where LID is not an entity that is searchable. The closest disease is “movement disorder” and “drug-induced dyskinesia.” Therefore, Open Targets is a promising open source tool for drug repositioning, but it is limited by the availability of database information on LID.

Project Rephetio is a direct drug repurposing tool available in the browser (het.io/repurpose) (Himmelstein et al., 2017). This engine is based on a large network dubbed Hetionet that integrates data from public resources to connect 11 features such as compounds, diseases, genes, ontologies and side effects through 24 types of relationships. Rephetio then uses a machine learning algorithm to identify network patterns that distinguish treatments from non-treatments and suggest novel drug therapies. The authors validate their algorithms by identifying drugs approved or in development for nicotine addiction and for epilepsy. In the browser, diseases are searchable by their Disease Ontology (Kibbe et al., 2014) accession number, where similar to OMIM, LID is unfortunately not available.

Finally, a methodology that does not rely on structured public data on LID, but relies instead on automatic analysis of the literature, is one that is available through IBM Watson. One of the modules of IBM Watson requires a known set of related concepts and then ranks candidate concepts by semantic similarity to the known set (Nagarajan et al., 2015; Spangler et al., 2014). This methodology has notably been recently employed to successfully predict novel RNA binding proteins altered in amyotrophic lateral sclerosis (Bakkar et al., 2017). In the case of drug repurposing, the known set is composed of drugs known to be effective against a disease of interest, and

the candidate set composed of other drugs to be ranked. Semantic similarity is computed by comparing relevant words and phrases often cited in concert with the drugs of interest in the biomedical literature. A 'graph diffusion' algorithm is then applied to score and rank each candidate drug by similarity to the entire known set. The advantages of this approach over other computational methods are that since the known drug set is curated by experts, the system does not need to have direct knowledge of LID and also that no structured data from external databases is necessary, indeed a semantic model can be created with only a handful, e.g. ~5.

For the known set for LID, we selected 15 compounds, of a range of classes and modes of actions, with demonstrated ability to reduce LID pre-clinically in animal models or in clinical trials. The classes of drugs included NMDA receptor antagonists, cannabinoid receptor 1/2 partial agonists, metabotropic glutamate receptor 5 (mGLUR5) negative allosteric modulators (NAM), AMPA receptor antagonists, alpha2 adrenergic receptor antagonists, serotonin 1A (5-HT1A) and serotonin 1B (5-HT1B) receptor agonists, alpha 7 containing nicotinic receptor agonists, alpha 4 beta 2 containing nicotinic receptor agonists, and mu/kappa-opioid receptor antagonists. It is worth noting that the known drugs reduce LID without affecting the beneficial effects of levodopa on PD. The candidate set was composed of 3539 drugs curated from the Drugbank database (www.drugbank.ca) and included FDA-approved small molecule or protein/peptide drugs, nutraceuticals and drugs in development. Dopamine agonists, antipsychotics and drugs with less than 5 published abstracts were filtered out of the list.

We then proceeded to validate the model in two different ways. First, a leave-one-out cross-validation of the known set was performed. The ranking was run 15 times, each time with one entity from the known set removed and instead added to the candidate set as the validation drug. The high ranking of the validation drugs in this exercise provided confidence in the model and suggested that highly ranked candidates from the final ranking would share many properties of the known set. Second, we validated the model through a retrospective study. The semantic similarity analysis was restricted to abstracts published up to and including the year 2013. Three known drugs with abstracts first demonstrating their anti-dyskinetic effects published after 2013 were omitted from the known set. Using only 7 and 4 available abstracts respectively, Watson's model ranked 2 drugs in the top 5.5% out of 3527 drugs and the third in the top 25%. Further proof of principle of the ability of IBM Watson to predict drugs with anti-dyskinetic efficacy is provided by our unpublished, pre-exiting data on pridopidine, which has properties to stabilize dopaminergic transmission in the central nervous system and is in development for Huntington disease (de Yebenes et al., 2011; Huntington Study Group, 2013; Kieburtz et al., 2017). In our study, IBM Watson ranked pridopidine 59/3527 candidate compounds (top 1.6%) representing a strong prediction of anti-dyskinetic efficacy. To date, there are no published data on Medline demonstrating anti-dyskinetic efficacy of pridopidine that might have driven its ranking high. However, as described above, pridopidine had been identified as a potential repurposing candidate based on analogy between LID and dyskinesia in Huntington's disease. We have subsequently shown that pridopidine significantly reduced LID in the MPTP-lesioned macaque model of Parkinson's disease (Johnston et al., 2017).

Another capability of IBM Watson is to mine documents to extract networks of relationships between concepts of interest using advanced natural language processing trained in the life sciences domain. While LID is not a disease in most databases, it was added to Watson's dictionary, enabling users to find connections between it and genes, proteins, drugs, and chemicals, in documents such as PubMed articles and patents. This capability allowed us to find connected genes/proteins between LID and top ranked candidate drugs, in order to evaluate common networks and pathways. In addition, this network of relationships forms the basis for another predictive module of IBM Watson, which we will not discuss in detail here. In brief, instead of ranking concepts by semantic similarity, concepts are scored and ranked based on a network algorithm inspired from recommender systems (matrix factorization) (Nagarajan et al., 2015). This module enables users to find novel relationships between drugs and LID directly, leveraging a model based on known relationships between drugs and diseases extracted from scientific documents and from structured databases when available.

In summary, many computational methodologies and tools are actively being developed for drug repurposing. Using these methodologies to identify novel treatments for LID poses a particular challenge due to its absence in most databases (such as disease-gene relationships, gene expression, medical records, etc.), due to its multiple known targets and pathways, and due to the fact that drugs for LID must not impede on the beneficial effects of levodopa on PD. These limitations have driven the authors to take a literature mining approach with IBM Watson, a methodology whose predictive ability was internally validated as well as proven with other studies.

4. How do we evaluate and prioritise repurposing candidates?

Thus far, this review has highlighted the problem of LID, the reasons it is a good indication for repurposing and shown that methodologies exist to identify repurposing candidates. Many criteria, both scientific and commercial, will come into play in prioritising these candidates. Commercial criteria include the cost of taking a project to market, this might depend on the data package available, the clinical development path to get to market and the level of protection that might be available if a product was marketed. Given that these are likely very specific to each compound, we will not address these issues further here. Rather, in this section, we will focus on the scientific issues that might be addressed pre-clinically and discuss why it is important to define how a drug might be deployed in LID and how the available animal models can offer insight into both efficacy and optimization of Phase II PoC design.

4.1. Choice of sub-indication within LID

The neural mechanisms underlying dyskinesia are not a single process (reviewed extensively here; (Picconi and Calabresi, 2017; Picconi et al., 2018)). 'Priming' refers to the molecular and behavioural sensitization events that occur after the first dose of L-DOPA. Priming need not always be associated with the expression of dyskinesia but, by definition, leads to alterations in the response to subsequent L-DOPA challenges that result in the emergence and 'expression" of overt dyskinesia and its subsequent development into a more severe phenotype. It is generally considered that once primed, the brain remains in that primed state, unless mechanisms are invoked to de-prime. Thus the brain is maintained "primed for LID", even when off the causative L-DOPA treatment (Huot et al., 2013; Iravani and Jenner, 2011; Jenner, 2008; Nadjar et al., 2009). Studies in which the ability of a novel therapeutic to impact LID is assessed typically fall into two broad categories based on how the experimental therapy, test item, may impact upon priming, development and expression of LID:

- prevent the development and/or maintenance of LID upon *de novo* L-DOPA administration and/or,
- be employed to reduce acute expression of LID once it has become established.

Additional indications may occasionally be considered within the context of LID, for example 'de-priming' studies whereby animals with pre-existing, established LID are treated with test item, with the goal of observing a lessening in LID severity with each subsequent L-DOPA challenge (Johnston et al., 2010a). The basic concepts pertaining to the two main categories of experiment described above are as follows:

Development of LID. Two or more groups of parkinsonian L-DOPA naïve, animals (typically unilateral 6-OHDA-lesioned rats or MPTP-lesioned NHP) will be treated with L-DOPA either alone (or rather in combination with vehicle) or in combination with test item and the effect on the genesis and development of LID assessed repeatedly over time (Visanji et al., 2009).

Established LID. Parkinsonian animals are treated chronically with L-DOPA for several weeks (rodents) or months (NHP) in the absence of test item, to evoke the established, stable expression of LID prior to assessment of the acute or chronic effect of a test compound when co-administered with L-DOPA (Bezard et al., 2004; Henry et al., 1999; Iravani et al., 2003; Johnston et al., 2010b). For each of these studies, the propensity of a potential therapeutic to influence expression of dyskinesia may be tested in various ways. Thus, an agent may act to reduce dyskinesia evoked by optimal or supra-optimal doses of L-DOPA that maximally reverse parkinsonian symptoms (Bezard et al., 2004; Johnston et al., 2010b; Morin et al., 2010). Alternatively, the ability of a therapeutic to enhance the anti-parkinsonian benefit afforded by threshold doses of L-DOPA that only partially alleviate symptoms whilst evoking less dyskinesia than that achieved by merely increasing L-DOPA dose (an L-DOPA 'sparing' effect) may also be assessed (Johnston et al., 2010c; Kanda et al., 2000).

When assessing the potential benefit of a novel test item, it may not be immediately obvious for which indication it may eventually be selected. However, it is always prudent to aim to assess both particularly since the mechanisms underlying different components of LID, whether 'priming' for LID or acute expression LID once established, are likely distinct, even if overlapping.

Regarding practical considerations, it is typically more rapid to assess the ability of acute administration of test items to reduce established LID since a single cohort of animals may be used with a crossover Latin-Square type design. This contrasts with studies examining the development of LID in which multiple parallel animal cohorts must be used along with repeat dosing throughout the period of L-DOPA administration (which may be many months in the case of experiments in old-world primates). This choice has obvious ramifications as to the cost of running the study, most critically in terms of number of animals but also related to the amount of test item required, staffing and total research budget considerations.

Detailed descriptions of the principal rodent and primate models of LID are reported and have been reviewed elsewhere (Breger et al., 2013; Fox and Brotchie, 2010; Jenner, 2003, 2009; Johnston and Lane, 2011; Morin et al., 2014) but are summarised below.

4.2. Rodent models of LID

The most widely-employed rodent models of LID are based upon a unilateral 6-hydroxydopamine (6-OHDA)-evoked unilateral lesion of the medial forebrain bundle, in rats or mice, which typically leads to a severe (>85% loss of striatal dopamine) and a stable lesion of the nigrostriatal tract (Ungerstedt and Arbuthnott, 1970). Administration of direct-acting dopamine agonists and L-DOPA stimulate supersensitive post-synaptic dopamine D2 receptors in the lesioned striatal hemisphere which evokes a contraversive rotational responses (Ungerstedt, 1971). With repeated L-DOPA treatment there is a progressive sensitization of rotational response such that successive L-DOPA administration evokes more rapid onset of rotations, increases in magnitude and a decrease in response duration when compared to the first day of treatment (Bevan, 1983; Deshaies et al., 1984). Decreases in peak numbers of net contraversive response evoked by L-DOPA have been used as an indication of anti-dyskinetic activity with purported classes of anti-dyskinetic compounds such as α2-adrenergic receptor antagonists also being effective at reducing LID in both primate models and humans (Henry et al., 1998; Lewitt et al., 2012; Savola et al., 2003). Thus, while rotational asymmetry is not dyskinesia *per se*, the underlying mechanism of the behaviour may at least in part be similar to that underlying LID and has proven useful in studying the molecular and cellular mechanisms of LID in Parkinson's disease (Visanji et al., 2009). However, a difficulty inherent to the interpretation of changes in magnitude of rotational asymmetry in this rodent model derives from understanding what proportion of the behaviour observed in response to L-DOPA might be considered therapeutic, i.e. anti-parkinsonian benefit and what proportion unwanted, i.e. LID. For example, application of a dopamine antagonist such as haloperidol decreases net contraversive rotations evoked by L-DOPA but necessarily acts to reduce both anti-parkinsonian and dyskinetic behaviours. In 1998, Cenci and colleagues proposed a method for the categorisation and rating of behaviours described as abnormal involuntary movements (AIMs) that are present, in addition to rotational asymmetry, in response to chronic L-DOPA administration (Cenci et al., 1998). The behaviours were divided into torsional twisting of the chest and abdomen (axial AIMs), rapid uncontrolled movements of the forelimb (limb AIMs) and rapid chewing motion of the orolingual area with tongue protrusions (orofacial AIMs) that, considered together, are known as ALO-AIMs. The potential utility of this phenotype was highlighted following pharmacological validation and demonstration that ALO-AIMs scores were significantly reduced in rat by the acute administration of compounds that have proven anti-dyskinetic efficacy in parkinsonian patients and/or NHP models of LID (Lundblad et al., 2002).

Regarding changes in either L-DOPA-induced rotational sensitivity and ALO-AIMs one issue to address is to ensure that a compound which decreases either of these behaviours is not negatively impacting on the anti-parkinsonian benefit of L-DOPA. For this reason, any compound that has been found to reduce either should ideally be assessed further to ensure lack of liability to negatively impact on L-DOPA-induced reversal of a behaviour related to parkinsonism, e.g. forelimb asymmetry, using either the cylinder or stepping tests (Schallert et al., 2000).

4.3. NHP models of LID

The L-DOPA-treated, MPTP-lesioned NHP remains the gold standard in terms of modelling LID. No current approach surpasses the fidelity with which the key behavioural phenomenology and underlying neurophysiological changes seen in PD patients with LID are reproduced. The MPTP-lesioned primate has been used frequently in the development of novel therapeutics predicting the efficacy and therapeutic outcome of novel dopaminergic (Jenner, 2009) and non-dopaminergic treatments (Fox et al., 2006), surgical (Aziz et al., 1991) and transplantation approaches (Bakay and Herring, 1989). The model has also been pivotal in helping delineate some of the mechanistic underpinnings of LID such as the role of the direct striatonigral and indirect striatopallidal pathways and subthalamic nucleus (STN) in regulating output regions of the basal ganglia in generating the motor symptoms of PD and LID (Crossman et al., 1985; DeLong et al., 1985; Wichmann and DeLong, 2003).

Differences in the phenomenology of the dyskinetic response to L-DOPA are apparent between various primates with some correlation between phylogenetic complexity of the species and the breadth of PD-like dyskinesias expressed. For instance, macaques readily express both choreiform and dystonic forms of dyskinesia (Boyce et al., 1990) whereas in the marmoset distinguishing the two types, while sometimes feasible, may be less straightforward (Fox and Brotchie, 2010).

Chronic treatment with L-DOPA in both PD patients and parkinsonian primates not only increases the severity of dyskinesia but modulates its temporal pattern of expression following acute challenge. Thus, upon first, *de novo,* administration of L-DOPA there is a graded reversal of parkinsonism and accompanying expression of dyskinesia as a product of increasing L-DOPA dose. In chronically treated animals, and in PD patients following long-term therapy, there is a more rapid anti-parkinsonian response (Nutt et al., 2002) and an 'all-or-nothing' dyskinetic effect in which increasing the dose of L-DOPA further fails to evoke a more severe dyskinetic response (Mestre et al., 2010). The MPTP-primate also successfully models the lack of separation of anti-parkinsonian and pro-dyskinetic properties of L-DOPA seen in chronically treated PD patients (Nutt et al., 2010). Following chronic dosing with L-DOPA in MPTP-lesioned NHPs, usually after several weeks or months of administration, dyskinesia is typically stable and reproducible between dosing (Pearce et al., 1995) thus allowing the reliable assessment of adjunct treatment on acute expression of LID (Johnston et al., 2010d).

Many studies have employed the MPTP-lesioned primate model to explore the pathogenesis underlying both parkinsonism and LID. These include investigations of the effect of dopaminergic denervation on the electrophysiology of basal ganglia nuclei (Wichmann and DeLong, 2003) and pre- and postsynaptic molecular mechanisms (Calabresi et al., 2010; Fasano et al., 2010; Hallett et al., 2005). In this regard, the primate model excels in being the closest representation both anatomically and in expression of pathological behavioural phenotype, to the human disease state. However, post-mortem studies of this type present significant cost and logistical challenges and most commonly are first investigated using rodent models. Perhaps more widely employed, the MPTP-lesioned primate remains without equal as an example of a neurological disease model for the assessment of novel therapeutics with potential to improve parkinsonian disability, either as monotherapy or as an adjunct to L-DOPA. With such expectation placed upon it, the ability of the MPTP-primate to inform and predict success in the clinic has been subjected to considerable scrutiny (reviewed by Fox et al., 2006). The MPTP-primate has been employed to optimise use of L-DOPA or dopamine agonists and thus informed clinical dosing paradigms that minimise the development and/or expression or motor complications of treatment (Jackson et al., 2007; Smith et al., 2005). Use of non-dopaminergic therapies in PD long preceded that of L-DOPA lending credence to a vast array of subsequent studies demonstrating the role of glutamate, serotonin, noradrenaline and other transmitters in the pathogenesis and expression of parkinsonian and dyskinetic behaviours. Examples of both translational successes such as the noradrenergic α_2 antagonist, fipamezole (Dimitrova et al., 2009; Johnston et al., 2010c) and the adenosine A_{2a} antagonists such as preladenant (Hauser et al., 2010; Hodgson et al., 2010) may be compared with application of opioid antagonists (Fox et al., 2004; Henry et al., 2001) or monoamine reuptake inhibitors (Frackiewicz et al., 2002; Pearce et al., 2002) that, while still affording considerable preclinical promise, have yet to be successfully applied in the clinic.

A well-designed and conducted NHP study with good evidence that treatments likely achieved appropriate target engagement should be used to make a hard go-nogo decision as to whether a compound is a candidate for progression to clinical development. The ability of a compound to provide anti-dyskinetic benefits in NHP without compromising anti-parkinsonian benefits of L-DOPA can likewise support a strong go-nogo decision for further investigation. The magnitude of anti-dyskinetic efficacy is an important criterion in prioritising multiple repurposing candidates.

5. How should we obtain clinical proof of concept?

In moving from a successful pre-clinical demonstration of efficacy to an optimal evaluation of PoC in the clinic, many factors need to be considered. Perhaps the most important is to appreciate the value of the NHP model and ensure that we have learned as many lessons as possible to inform translation to the clinic. At the heart of the first clinical PoC study should be the goal to confirm the finding of the NHP study. Thus, as much as is feasible, the clinical PoC study should replicate the NHP study in terms of endpoints, treatment regimen and levels and selectivity of target engagement. Although effect sizes cannot always be translated across species, the PoC study can be powered to demonstrate minimal changes of equivalent magnitude to those seen, on similar endpoints used in the NHP. It is also important to remember that the NHP studies are performed to prioritise candidates on the basis of potential efficacy and little data on tolerability in the LID patient population may have been obtained previously. Likewise, even though a repurposed drug will likely have a good human safety package, tolerability in the PD population cannot necessarily be inferred from different patients or healthy volunteer populations.

The primary endpoint in all studies will be a specific clinical measure of LID. There are three classes of rating that can be potentially applied in clinical studies of LID,

- physician-administered, objective clinical rating scales for severity and disability;
- subjective, patient-reported disability for activities of daily living (ADLs), and,
- patient-reported home diaries for amount of awake time associated with LID.

There are several objective physician-administered clinical scales in use, including the Abnormal Involuntary Movement Scale (AIMS), the Obeso Dyskinesia Rating Scale, the Rush Dyskinesia Rating Scale, the Clinical Dyskinesia Rating Scale (CDRS), and the motor portion, part III, of the Unified Dyskinesia Rating Scale (UDysRS) (reviewed in (Colosimo et al., 2010)). These were evaluated by a task force from the International Parkinson and Movement Disorder Society (MDS) for ease of use and clinimetrics; the UDysRS was ranked as the most valid in PD (Colosimo et al., 2010). All these rating scales require training, and accuracy and variability of evaluations may impact endpoint ratings. Ongoing increased use of the UDysRS in DBRCTs will evaluate its usefulness but it is the most attractive scale currently available for use in Phase II PoCs for repurposed drugs. We consider categorical rating of LID in NHP, as described with the NHPDysRs, e.g. as employed in (Johnston et al., 2010b, 2010c, 2017), to be analogous to the motor component of UDysRs, and thus UDysRS is likely the optimal scale for use in translating effects on LID in NHP that were most profound on that scale.

Subjective patient reported scales for dyskinesia include the MDS-Unified Parkinson's Disease Rating Scale (UPDRS) part IV; the Lang-Fahn Activities of Daily Living Dyskinesia Scale, the Parkinson Disease Dyskinesia Scale (PDYS-26), and UDysRS patient-reported sections. The PDY-26 and UDyRS are considered to be

the most valid and with certain treatment regimens, e.g. multi-week treatments, could have value in Phase II PoC for repurposed agents (Colosimo et al., 2010). Although, clearly, not subject-reported, an NHP equivalent of MDS-UPDRS IV, item 34 has been described (Johnston et al., 2013), which could be of value in NHP studies to guide whether the use of these clinical endpoints might add value to the PoC studies.

The Hauser diary is the most commonly-used PD patient home diary (Hauser et al., 2000) and is a patient-completed assessment of percentage of time during the waking day as 'OFF' and 'ON' periods; 'with' and 'without LID'. Several options exist for the LID evaluation and patients may be instructed to note the perceived level of disability of the dyskinesia i.e. 'bothersome' vs 'non-bothersome dyskinesia'. In all studies, secondary endpoints include measures of PD motor disability, most commonly using the MDS-UPDRS II (ADLs) and III (Motor). This is critical to ensure that reductions in LID are not at the expense of worsening PD motor function. However, with respect to the present discussion, it should be noted that while such diaries are uniformly used across the majority of Phase III studies, they are rarely employed in Phase II PoC. This notwithstanding, in recent years, attempts have been made to develop endpoints in NHP which might interrogate processes similar to the diary measures clinically. Thus, while NHP assessment cannot evaluate "bothersome" LID equivalency of diary endpoints this aim might be approximated by measures of "on-time with disabling LID" or "on-time without dyskinesia" in NHP (Fox et al., 2012). If, in NHP studies, these types of endpoints are particularly sensitive to a specific test item then, if appropriate for the dosing regimen, i.e. not acute challenge, it might be prudent to consider including a subjective diary measure in the clinical PoC study.

Thus, while multiple endpoints can be employed in a Phase II PoC, in selecting the primary endpoint and driving the power calculation, if at all possible, the endpoint most equivalent to that showing the main efficacy effect in NHP should be employed. In many cases this is clear, there are NHP equivalents of the objective components of the UDysRS and UPDRS IV item 34. However, while subjective reports cannot be obtained in pre-clinical studies, attempts have been made to develop scales in NHP that could inform endpoint selection in the clinic.

The basic design of the clinical PoC study of a repurposing candidate also needs careful consideration. Of course, as is clear from the above discussion, recapitulating the successful NHP study is, for us, a key consideration. To date, there does not appear to be a preferred method and determination of the optimal dose for Phase II PoC studies. The gold standard would be to ensure that the drug exposures and target engagement achieved at Phase II, equal, or exceed, those providing anti-dyskinetic efficacy in NHP. Without this, no negative PoC study can be interpreted with confidence. Unfortunately, this standard is rarely met. At a bare minimum, we seek to ensure that plasma exposure levels that provided efficacy in NHP are achieved in the clinical PoC. Another factor that may reduce accuracy of measuring LID is the inherent fluctuating nature of PD. Thus, an in-hospital objective assessment of LID by the physician to rate the severity and disability, using a rating scale, may vary in the same patient taking the same dose of L-DOPA, and reflects the day-to day variability of LID. The simple change in environment from home to hospital is just one external stressor that may increase the level of LID. Other factors include variable gastrointestinal function in PD, affecting absorption of L-DOPA etc. that may all add to variability of baseline LID measured in a hospital clinic setting. One approach to address this problem is to conduct PoC studies where the subject visits the study site, after stopping all PD treatments the previous evening, i.e. in the practically-defined off-state and then is administered L-DOPA at a suprathreshold dose (equivalent to their normal morning L-DOPA dose, plus 25%). This approach should ensure the subject switches on and LID is elicited in the test situation as has been successfully employed in several PoC studies (Carroll et al., 2004; Svenningsson et al., 2015). To further reduce this variability in oral levodopa absorption, i.v. infusions of L-DOPA have been used to obtain a more predictable on-state, and reduce variability in level of LID (Fox et al., 2017). Another important factor is that there is often a discrepancy between the objective physician rated accuracy of amount of LID vs the patient's perception in their home environment. For this reason, we propose that the primary purpose of a Phase II PoC should be to determine if the effects on LID in NHP can be translated to PD. The understanding of the magnitude of clinical benefit may need to await further investigation, and for a repurposed agent this might not be fully achieved until post-approval. To try and improve this discord between objective and subjective measures of LID, and potentially empower the clinical PoC study to better estimate clinical benefit, estimation of a "clinically-meaningful change" have been proposed (Mestre et al., 2015). This could then allow the rigor of the clinical rating by the physician to equate into a patient-relevant change. For clinical trials it also allows a better power calculation to determine number of subjects required for statistical validity.

Improvements in measurement of LID may emerge from to advances in technology, for instance, a wearable device easily worn by the patient at home that provides a measure of limb/trunk movement that correlates with level of LID. Reported methods have ranged from patient-worn devices (Lopane et al., 2015; Ramsperger et al., 2016) to post-hoc video analysis methods (Li et al., 2017). Several studies are in progress and may allow some objective measure but, to date, we do not consider that these have not shown enough specificity and sensitivity to replace clinical assessments (Del Din et al., 2016; Espay et al., 2016). As with rating scales, it will be a major advance in translating the success of repurposing candidates if the same wearables can be deployed in both NHP and human.

A final disease-related factor that makes these studies uniquely challenging, and the translation from NHP to clinical PoC, is the large placebo effect seen in PD subjects in RCTs. Thus, simply enrolling a PD subject with LID into a clinical study and administering placebo will reduce the level of LID by 30–50%, e.g. the purported $5HT_{1A}$ agonist, sarizotan trials, reported reduced ON time with LID of up to 1.5 h/d in placebo groups compared to average 2 h/d with drug (Goetz et al., 2008). New concepts of 'placebo run-in; have been introduced into some PD studies (Murata et al., 2018) but to date, not in a trial for an agent targeting LID.

6. Concluding remarks

LID remains a largely unmet need but represents a particularly opportune indication for drug repurposing. At this juncture, we have a reasonable scientific understanding of the pathological mechanisms underlying LID and this has given rise to a range of promising potential targets for therapeutic intervention. Alongside these traditional methods, novel AI-driven computational approaches offer a means to drive drug discovery. Development of new therapies for LID also benefits from a range of excellent animal models with a proven track record of predictive validity in translation of efficacy to success at Phase II PoC. Well established clinical PoC methodologies are available to quickly and cost-effectively provide preliminary data with which to gate progress to larger trials or even directly to regulatory submission. Lastly, the regulatory climate has become increasingly receptive with nascent development programs being able to gain orphan drug designation for the treatment of LID with resultant benefits

in terms of reduced financial, legal and intellectual property incentives that this brings.

Our own perspective is that an optimal approach to successfully develop any repurposing candidate would be a step-wise one whereby, following identification of such a candidate therapy, we first evaluate efficacy in a rodent model of LID. This would allow prioritisation and an initial guide to dose and target engagement levels associated with efficacy. Such data would guide the design of studies in the MPTP-lesioned NHP. Efficacy in the primate would provide the basis for a hard go-nogo decision to proceed to clinical PoC. Ideally one should obtain a measure of target engagement or at least a robust understanding of plasma exposure levels associated with efficacy in the primate. These key data can then be used to ensure equivalency in humans before designing a clinical PoC study that truly mimics and allows for recapitulation of the successful primate study both in terms of target engagement and the specific measures of LID chosen as endpoints.

Acknowledgements

The authors would like to thank the Ontario Brain Institute for their financial support of the use of IBM Watson in the included case study.

References

Anichtchik, O.V., Peitsaro, N., Rinne, J.O., Kalimo, H., Panula, P., 2001. Distribution and modulation of histamine H(3) receptors in basal ganglia and frontal cortex of healthy controls and patients with Parkinson's disease. Neurobiol. Dis. 8, 707–716.

Ashburn, A., Stack, E., Pickering, R.M., Ward, C.D., 2001. A community-dwelling sample of people with Parkinson's disease: characteristics of fallers and non-fallers. Age Ageing 30, 47–52.

Aziz, T.Z., Peggs, D., Sambrook, M.A., Crossman, A.R., 1991. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov. Disord. 6, 288–292.

Bachmann, C.G., Trenkwalder, C., 2006. Body weight in patients with Parkinson's disease. Mov. Disord. 21, 1824–1830.

Bajjalieh, S.M., Peterson, K., Linial, M., Scheller, R.H., 1993. Brain contains two forms of synaptic vesicle protein 2. Proc. Natl. Acad. Sci. U. S. A. 90, 2150–2154.

Bakay, R.A., Herring, C.J., 1989. Central nervous system grafting in the treatment of parkinsonism. Stereotact. Funct. Neurosurg. 53, 1–20.

Bakkar, N., Kovalik, T., Lorenzini, I., Spangler, S., Lacoste, A., Sponaugle, K., Ferrante, P., Argentinis, E., Sattler, R., Bowser, R., 2017. Artificial intelligence in neurodegenerative disease research: use of IBM Watson to identify additional RNA-binding proteins altered in amyotrophic lateral sclerosis. Acta Neuropathol. 124, 339.

Ban, T.A., 2006. The role of serendipity in drug discovery. Dialogues Clin. Neurosci. 8, 335–344.

Bara-Jimenez, W., Bibbiani, F., Morris, M.J., Dimitrova, T., Sherzai, A., Mouradian, M.M., Chase, T.N., 2005. Effects of serotonin 5-HT1A agonist in advanced Parkinson's disease. Mov. Disord. 20, 932–936.

Barnum, C.J., Bhide, N., Lindenbach, D., Surrena, M.A., Goldenberg, A.A., Tignor, S., Klioueva, A., Walters, H., Bishop, C., 2012. Effects of noradrenergic denervation on L-DOPA-induced dyskinesia and its treatment by alpha- and beta-adrenergic receptor antagonists in hemiparkinsonian rats. Pharmacol. Biochem. Behav. 100, 607–615.

Barrett, T., Wilhite, S.E., Ledoux, P., Evangelista, C., Kim, I.F., Tomashevsky, M., Marshall, K.A., Phillippy, K.H., Sherman, P.M., Holko, M., Yefanov, A., Lee, H., Zhang, N., Robertson, C.L., Serova, N., Davis, S., Soboleva, A., 2012. NCBI GEO: archive for functional genomics data sets—update. Nucleic Acids Res. 41, D991–D995.

Bartoszyk, G.D., Van Amsterdam, C., Greiner, H.E., Rautenberg, W., Russ, H., Seyfried, C.A., 2004. Sarizotan, a serotonin 5-HT1A receptor agonist and dopamine receptor ligand. 1. Neurochemical profile. J. Neural. Transm. 111, 113–126.

Bedard, P.J., Di Paolo, T., Falardeau, P., 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.

Bertrand, D., Chng, K.R., Sherbaf, F.G., Kiesel, A., Chia, B.K.H., Sia, Y.Y., Huang, S.K., Hoon, D.S.B., Liu, E.T., Hillmer, A., Nagarajan, N., 2015. Patient-specific driver gene prediction and risk assessment through integrated network analysis of cancer omics profiles. Nucleic Acids Res. 43, e44–e44.

Betts, T., Waegemans, T., Crawford, P., 2000. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 9, 80–87.

Bevan, P., 1983. Repeated apomorphine treatment causes behavioural supersensitivity and dopamine D2 receptor hyposensitivity. Neurosci. Lett. 35, 185–189.

Bezard, E., Hill, M.P., Crossman, A.R., Brotchie, J.M., Michel, A., Grimee, R., Klitgaard, H., 2004. Levetiracetam improves choreic levodopa-induced dyskinesia in the MPTP-treated macaque. Eur. J. Pharmacol. 485, 159–164.

Bezard, E., Tronci, E., Pioli, E.Y., Li, Q., Porras, G., Bjorklund, A., Carta, M., 2013. Study of the antidyskinetic effect of eltoprazine in animal models of levodopa-induced dyskinesia. Mov. Disord. 28, 1088–1096.

Bibbiani, F., Oh, J.D., Chase, T.N., 2001. Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models. Neurology 57, 1829–1834.

Blanchet, P.J., Konitsiotis, S., Chase, T.N., 1998. Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. Mov. Disord. 13, 798–802.

Bordia, T., Campos, C., Huang, L., Quik, M., 2008. Continuous and intermittent nicotine treatment reduces L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. J. Pharmacol. Exp. Therapeut. 327, 239–247.

Boyce, S., Clarke, C.E., Luquin, R., Peggs, D., Robertson, R.G., Mitchell, I.J., Sambrook, M.A., Crossman, A.R., 1990. Induction of chorea and dystonia in parkinsonian primates. Mov. Disord. 5, 3–7.

Boyd, E.M., 1946. The cough syrup. Br. Med. J. 2, 735.

Braun, M.M., Farag-El-Massah, S., Xu, K., Cote, T.R., 2010. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nat. Rev. Drug Discov. 9, 519–522.

Breger, L.S., Dunnett, S.B., Lane, E.L., 2013. Comparison of rating scales used to evaluate L-DOPA-induced dyskinesia in the 6-OHDA lesioned rat. Neurobiol. Dis. 50, 142–150.

Bristow, L.J., Kramer, M.S., Kulagowski, J., Patel, S., Ragan, C.I., Seabrook, G.R., 1997. Schizophrenia and L-745,870, a novel dopamine D4 receptor antagonist. Trends Pharmacol. Sci. 18, 186–188.

Brotchie, J.M., Johnston, T.H., Fox, S.H., Zerr, P., Tiberghein, F., 2007. FP0011 extends the duration of the anti-parkinsonian actions of L-DOPA and reduces L-DOPA-induced dyskinesia in the MPTP-lesiones macaque model of Parkinson's Disease. Mov. Disord. 22, S95.

Budd, K., 1987. Clinical use of opioid antagonists. Bailliere. Clin. Anaesthesiol. 1, 993–1011.

Calabresi, P., Di Filippo, M., Ghiglieri, V., Tambasco, N., Picconi, B., 2010. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. Lancet Neurol. 9, 1106–1117.

Calon, F., Birdi, S., Rajput, A.H., Hornykiewicz, O., Bedard, P.J., Di Paolo, T., 2002. Increase of preproenkephalin mRNA levels in the putamen of Parkinson disease patients with levodopa-induced dyskinesias. J. Neuropathol. Exp. Neurol. 61, 186–196.

Carey, R.J., 1991. Naloxone reverses L-dopa induced overstimulation effects in a Parkinson's disease animal model analogue. Life Sci. 48, 1303–1308.

Carroll, C.B., Bain, P.G., Teare, L., Liu, X., Joint, C., Wroath, C., Parkin, S.G., Fox, P., Wright, D., Hobart, J., Zajicek, J.P., 2004. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. Neurology 63, 1245–1250.

Cenci, M.A., Lee, C.S., Bjorklund, A., 1998. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. Eur. J. Neurosci. 10, 2694–2706.

Charles, O., Coolsaet, B., 1972. Prevention of hemorrhage in prostatic surgery. Apropos of the study of the hemostatic activity in prostatectomy of a new molecule: beta-naphthoquinone monosemicarbazone (Naftazone). Ann. Urol (Paris) 6, 209–212.

Clarke, C.E., Sambrook, M.A., Mitchell, I.J., Crossman, A.R., 1987. Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). J. Neurol. Sci. 78, 273–280.

Colosimo, C., Martinez-Martin, P., Fabbrini, G., Hauser, R.A., Merello, M., Miyasaki, J., Poewe, W., Sampaio, C., Rascol, O., Stebbins, G.T., Schrag, A., Goetz, C.G., 2010. Task force report on scales to assess dyskinesia in Parkinson's disease: critique and recommendations. Mov. Disord. 25, 1131–1142.

Crockett, S.D., Schectman, R., Stürmer, T., Kappelman, M.D., 2014. Topiramate use does not reduce flares of inflammatory bowel disease. Dig. Dis. Sci. 59, 1535–1543.

Crossman, A.R., Mitchell, I.J., Sambrook, M.A., 1985. Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. Neuropharmacology 24, 587–591.

Daneault, J.F., Carignan, B., Sadikot, A.F., Panisset, M., Duval, C., 2013. Drug-induced dyskinesia in Parkinson's disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia?. BMC Med. 11, 76.
Davies, W.L., Grunert, R.R., Haff, R.F., McGahen, J.W., Neumayer, E.M., Paulshock, M., Watts, J.C., Wood, T.R., Hermann, E.C., Hoffmann, C.E., 1964. Antiviral activity of 1-adamantanamine (amantadine). Science 144, 862–863.
de Yebenes, J.G., Landwehrmeyer, B., Squitieri, F., Reilmann, R., Rosser, A., Barker, R.A., Saft, C., Magnet, M.K., Sword, A., Rembratt, A., Tedroff, J., Mermai, H. D. s. i., 2011. Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 10, 1049–1057.
Deane, K.H., Flaherty, H., Daley, D.J., Pascoe, R., Penhale, B., Clarke, C.E., Sackley, C., Storey, S., 2014. Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease. BMJ Open 4, e006434.
Dekundy, A., Lundblad, M., Danysz, W., Cenci, M.A., 2007. Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model. Behav. Brain Res. 179, 76–89.
Del Din, S., Godfrey, A., Galna, B., Lord, S., Rochester, L., 2016. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. J. NeuroEng. Rehabil. 13, 46.
DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281–285.
DeLong, M.R., Crutcher, M.D., Georgopoulos, A.P., 1985. Primate globus pallidus and subthalamic nucleus: functional organization. J. Neurophysiol. 53, 530–543.
Deshaies, P., Bedard, P., Falardeau, P., Di Paolo, T., 1984. Behavioral and biochemical evidence of apomorphine-induced supersensitivity of the striatal dopamine receptors. Neuropharmacology 23, 1219–1222.
Dimitrova, T.D., Bara-Jimenez, W., Savola, J.M., Encarnacion, E.V., Mouradian, M.M., Chase, T.N., 2009. Alpha-2 adrenergic antagonist effects in Parkinson's disease. In: Movement Disorder Society's Thirteenth International Congress of Parkinson's Disease and Movement Disorders, Paris, France, Mo-199.
Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R., Lozano, A.M., 2000. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J. Neurophysiol. 84, 570–574.
Drury, A.N., Iliescu, C.C., 1921. The restoration of the normal cardiac mechanism in cases of auricular fibrillation by means of quinidine sulphate. Br. Med. J. 2, 511–514.
Du, H., Nie, S., Chen, G., Ma, K., Xu, Y., Zhang, Z., Papa, S.M., Cao, X., 2015. Levetiracetam ameliorates l-dopa-induced dyskinesia in hemiparkinsonian rats inducing critical molecular changes in the striatum. Parkinsons Dis 2015, 253878.
Dudley, J.T., Sirota, M., Shenoy, M., Pai, R.K., Roedder, S., Chiang, A.P., Morgan, A.A., Sarwal, M.M., Pasricha, P.J., Butte, A.J., 2011. Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Sci. Transl. Med. 3, 96ra76-96ra76.
Durif, F., Debilly, B., Galitzky, M., Morand, D., Viallet, F., Borg, M., Thobois, S., Broussolle, E., 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, A.M., Agid, Y., 1997. Low-dose clozapine improves dyskinesias in Parkinson's disease. Neurology 48, 658–662.
Elliott, H.W., Navarro, G., Nomof, N., 1970. A double blind controlled study of the pharmacologic effects of nalbuphine (EN-2234A). J. Med. 1, 74–89.
Engber, T.M., Susel, Z., Kuo, S., Gerfen, C.R., Chase, T.N., 1991. Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats. Brain Res. 552, 113–118.
Espay, A.J., Bonato, P., Nahab, F.B., Maetzler, W., Dean, J.M., Klucken, J., Eskofier, B.M., Merola, A., Horak, F., Lang, A.E., Reilmann, R., Giuffrida, J., Nieuwboer, A., Horne, M., Little, M.A., Litvan, I., Simuni, T., Dorsey, E.R., Burack, M.A., Kubota, K., Kamondi, A., Godinho, C., Daneault, J.F., Mitsi, G., Krinke, L., Hausdorff, J.M., Bloem, B.R., Papapetropoulos, S., Movement Disorders Society Task Force on, T, 2016. Technology in Parkinson's disease: challenges and opportunities. Mov. Disord. 31, 1272–1282.
Fang, J., Wang, L., Li, Y., Lian, W., Pang, X., Wang, H., Yuan, D., Wang, Q., Liu, A.-L., Du, G.-H., 2017. AlzhCPI: a knowledge base for predicting chemical-protein interactions towards Alzheimer's disease. PLoS One 12, e0178347–0178316.
Fasano, S., Bezard, E., D'Antoni, A., Francardo, V., Indrigo, M., Qin, L., Dovero, S., Cerovic, M., Cenci, M.A., Brambilla, R., 2010. Inhibition of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) signaling in the striatum reverts motor symptoms associated with L-dopa-induced dyskinesia. Proc. Natl. Acad. Sci. U. S. A.
Felder, C.C., Nielsen, A., Briley, E.M., Palkovits, M., Priller, J., Axelrod, J., Nguyen, D.N., Richardson, J.M., Riggin, R.M., Koppel, G.A., Paul, S.M., Becker, G.W., 1996. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. FEBS Lett. 393, 231–235.
Fink, M., Zaks, A., Sharoff, R., Mora, A., Bruner, A., Levit, S., Freedman, A.M., 1968. Naloxone in heroin dependence. Clin. Pharmacol. Ther. 9, 568–577.
Fleischhacker, W.W., Buchgeher, A., Schubert, H., 1986. Memantine in the treatment of senile dementia of the Alzheimer type. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 10, 87–93.
Fox, S., Silverdale, M., Kellett, M., Davies, R., Steiger, M., Fletcher, N., Crossman, A., Brotchie, 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, S.H., Brotchie, J.M., 2010. The MPTP-lesioned non-human primate models of Parkinson's disease. Past, present, and future. Prog. Brain Res. 184, 133–157.
Fox, S.H., Henry, B., Hill, M., Crossman, A., Brotchie, 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, S.H., Henry, B., Hill, M.P., Peggs, D., Crossman, A.R., Brotchie, J.M., 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, S.H., Johnston, T.H., Li, Q., Brotchie, J., Bezard, E., 2012. A critique of available scales and presentation of the non-human primate dyskinesia rating scale. Mov. Disord. 27, 1373–1378.
Fox, S.H., Katzenschlager, R., Lim, S.Y., Barton, B., de Bie, R.M.A., Seppi, K., Coelho, M., Sampaio, C., Movement Disorder Society Evidence-Based Medicine, C, 2018. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov. Disord.
Fox, S.H., Katzenschlager, R., Lim, S.Y., Ravina, B., Seppi, K., Coelho, M., Poewe, W., Rascol, O., Goetz, C.G., Sampaio, C., 2011. The movement disorder society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. Mov. Disord. 26 (Suppl. 3), S2–S41.
Fox, S.H., Lang, A.E., Brotchie, J.M., 2006. 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, S.H., Metman, L.V., Nutt, J.G., Brodsky, M., Factor, S.A., Lang, A.E., Pope, L.E., Knowles, N., Siffert, J., 2017. Trial of dextromethorphan/quinidine to treat levodopa-induced dyskinesia in Parkinson's disease. Mov. Disord. 32, 893–903.
Frackiewicz, E.J., Jhee, S.S., Shiovitz, T.M., Webster, J., Topham, C., Dockens, R.C., Whigan, D., Salazar, D.E., Cutler, N.R., 2002. Brasofensine treatment for Parkinson's disease in combination with levodopa/carbidopa. Ann. Pharmacother. 36, 225–230.
Ghaemi, S.N., Katzow, J.J., 1999. The use of quetiapine for treatment-resistant bipolar disorder: a case series. Ann. Clin. Psychiatr. 11, 137–140.
Ghiglieri, V., Mineo, D., Vannelli, A., Cacace, F., Mancini, M., Pendolino, V., Napolitano, F., di Maio, A., Mellone, M., Stanic, J., Tronci, E., Fidalgo, C., Stancampiano, R., Carta, M., Calabresi, P., Gardoni, F., Usiello, A., Picconi, B., 2016. Modulation of serotonergic transmission by eltoprazine in L-DOPA-induced dyskinesia: behavioral, molecular, and synaptic mechanisms. Neurobiol. Dis. 86, 140–153.
Goetz, C.G., Damier, P., Hicking, C., Laska, E., Muller, T., Olanow, C.W., Rascol, O., 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, C.G., Laska, E., Hicking, C., Damier, P., Muller, T., Nutt, J., Warren Olanow, C., Rascol, O., Russ, H., 2008. Placebo influences on dyskinesia in Parkinson's disease. Mov. Disord. 23, 700–707.
Gomez-Mancilla, B., Bedard, P.J., 1993. Effect of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. Clin. Neuropharmacol. 16, 418–427.
Gomez-Ramirez, J., Johnston, T.H., Visanji, N.P., Fox, S.H., Brotchie, J.M., 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.
Gregoire, L., Samadi, P., Graham, J., Bedard, P.J., Bartoszyk, G.D., Di Paolo, T., 2009. Low doses of sarizotan reduce dyskinesias and maintain antiparkinsonian efficacy of L-Dopa in parkinsonian monkeys. Park. Relat. Disord. 15, 445–452.
Grondin, R., Doan, V.D., Gregoire, L., Bedard, P.J., 1999. D1 receptor blockade improves L-dopa-induced dyskinesia but worsens parkinsonism in MPTP monkeys. Neurology 52, 771–776.
Grondin, R., Hadj Tahar, A., Doan, V.D., Ladure, P., Bedard, P.J., 2000. Noradrenoceptor antagonism with idazoxan improves L-dopa-induced dyskinesias in MPTP monkeys. Naunyn-Schmiedeberg's Arch. Pharmacol. 361, 181–186.
Grossman, F., Potter, W.Z., Brown, E.A., Maislin, G., 1999. A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. J. Affect. Disord. 56, 237–243.
Hallett, P.J., Dunah, A.W., Ravenscroft, P., Zhou, S., Bezard, E., Crossman, A.R., Brotchie, J.M., Standaert, D.G., 2005. Alterations of striatal NMDA receptor subunits associated with the development of dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. Neuropharmacology 48, 503–516.
Harden, C.L., 1994. New antiepileptic drugs. Neurology 44, 787–795.

Hauser, R.A., Friedlander, J., Zesiewicz, T.A., Adler, C.H., Seeberger, L.C., O'Brien, C.F., Molho, E.S., Factor, S.A., 2000. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin. Neuropharmacol. 23, 75–81.

Hauser, R.A., Pourcher, E., Micheli, F., Mok, V., Onofrj, M., Huyck, S.B., Wolski, K., Cantillon, M., 2010. Efficacy of preladenant, a novel A2A antagonist, as an adjunct to levodopa for the treatment of Parkinson's disease. Mov. Disord. 24 (Suppl. 1), S265.

Hely, M.A., Morris, J.G., Reid, W.G., Trafficante, R., 2005. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov. Disord. 20, 190–199.

Henry, B., Crossman, A.R., Brotchie, J.M., 1998. Characterization of enhanced behavioral responses to L-DOPA following repeated administration in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Exp. Neurol. 151, 334–342.

Henry, B., Duty, S., Fox, S.H., Crossman, A.R., Brotchie, J.M., 2003. Increased striatal pre-proenkephalin B expression is associated with dyskinesia in Parkinson's disease. Exp. Neurol. 183, 458–468.

Henry, B., Fox, S.H., Crossman, A.R., Brotchie, J.M., 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, S.H., Peggs, D., Crossman, A.R., Brotchie, J.M., 1999. The alpha2-adrenergic receptor antagonist idazoxan reduces dyskinesia and enhances anti-parkinsonian actions of L-dopa in the MPTP-lesioned primate model of Parkinson's disease. Mov. Disord. 14, 744–753.

Hill, M.P., Bezard, E., McGuire, S.G., Crossman, A.R., Brotchie, J.M., Michel, A., Grimee, R., 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.

Himmelstein, D.S., Lizee, A., Hessler, C., Brueggeman, L., Chen, S.L., Hadley, D., Green, A., Khankhanian, P., Baranzini, S.E., 2017. Systematic integration of biomedical knowledge prioritizes drugs for repurposing. eLife 6, e26726–26735.

Hodgson, R.A., Bedard, P.J., Varty, G.B., Kazdoba, T.M., Di Paolo, T., Grzelak, M.E., Pond, A.J., Hadjtahar, A., Belanger, N., Gregoire, L., Dare, A., Neustadt, B.R., Stamford, A.W., Hunter, J.C., 2010. Preladenant, a selective A(2A) receptor antagonist, is active in primate models of movement disorders. Exp. Neurol. 225, 384–390.

Huang, L.Z., Campos, C., Ly, J., Ivy Carroll, F., Quik, M., 2011. Nicotinic receptor agonists decrease L-dopa-induced dyskinesias most effectively in partially lesioned parkinsonian rats. Neuropharmacology

Huang, Y.-F., Yeh, H.-Y., Soo, V.-W., 2013. Inferring drug-disease associations from integration of chemical, genomic and phenotype data using network propagation. BMC Med. Genom. 6 (Suppl. 3), S4.

Hub, P.I., 2015. Drug Discovery and Development: Understanding the R&D Process.

Huntington Study Group, H.I., 2013. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. Mov. Disord. 28, 1407–1415.

Huot, P., Johnston, T.H., Koprich, J.B., Aman, A., Fox, S.H., Brotchie, J.M., 2012a. L-745,870 reduces L-3,4-dihydroxyphenylylalanine-induced dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. J. Pharmacol. Exp. Therapeut.jpet.112.195693 [pii]195610.191124/jpet.195112.195693.

Huot, P., Johnston, T.H., Koprich, J.B., Aman, A., Fox, S.H., Brotchie, J.M., 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. Therapeut. 342, 576–585.

Huot, P., Johnston, T.H., Koprich, J.B., Fox, S.H., Brotchie, J.M., 2012c. The pharmacology of l-dopa-induced dyskinesia in Parkinson's disease. Pharmacol. Rev. 65, 171–222.

Huot, P., Johnston, T.H., Koprich, J.B., Fox, S.H., Brotchie, J.M., 2013. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. Pharmacol. Rev. 65, 171–222.

Iorio, F., Bosotti, R., Scacheri, E., Belcastro, V., Mithbaokar, P., Ferriero, R., Murino, L., Tagliaferri, R., Brunetti-Pierri, N., Isacchi, A., di Bernardo, D., 2010. Discovery of drug mode of action and drug repositioning from transcriptional responses. Proc. Natl. Acad. Sci. U.S.A. 107, 14621–14626.

Iravani, M.M., Jackson, M.J., Kuoppamaki, M., Smith, L.A., 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, M.M., Jenner, P., 2011. Mechanisms underlying the onset and expression of levodopa-induced dyskinesia and their pharmacological manipulation. J. Neural. Transm. (Vienna) 118, 1661–1690.

Jackson, M.J., Smith, L.A., Al-Barghouthy, G., Rose, S., Jenner, P., 2007. Decreased expression of l-dopa-induced dyskinesia by switching to ropinirole in MPTP-treated common marmosets. Exp. Neurol. 204, 162–170.

Jenner, P., 2003. The contribution of the MPTP-treated primate model to the development of new treatment strategies for Parkinson's disease. Park. Relat. Disord. 9, 131–137.

Jenner, P., 2008. Molecular mechanisms of L-DOPA-induced dyskinesia. Nat. Rev. Neurosci. 9, 665–677.

Jenner, P., 2009. From the MPTP-treated primate to the treatment of motor complications in Parkinson's disease. Park. Relat. Disord. 15 (Suppl. 4), S18–S23.

Jimenez, A., Marin, C., Bonastre, M., Tolosa, E., 1999. Narrow beneficial effect of dextromethorphan on levodopa-induced motor response alterations in an experimental model of parkinsonism. Brain Res. 839, 190–193.

Johnston, T.H., Damude, S., Huot, P., Fox, S.H., Jones, S.W., Rusche, J.R., Brotchie, J.M., 2010a. The Histone Deacetylase (HDAC) Inhibitor RGFP109 Reverses Established Motor Complications in L-dopa-treated Parkinsonian Primates Society for Neuroscience, 749.715.

Johnston, T.H., Fox, S.H., McIldowie, M.J., Piggott, M.J., Brotchie, J.M., 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. Therapeut. 333, 865–873.

Johnston, T.H., Fox, S.H., Piggott, M.J., Savola, J.M., Brotchie, J.M., 2010c. The alpha adrenergic antagonist fipamezole improves quality of levodopa action in Parkinsonian primates. Mov. Disord. 25, 2084–2093.

Johnston, T.H., Geva, M., Steiner, L., Orbach, A., Papapetropoulos, S., Savola, J.M., Reynolds, I.J., Ravenscroft, P., Hill, M.P., Fox, S.H., Brotchie, J.M., Hayden, M., 2017. Pridopidine, a clinical trial-ready compound, reduces L-DOPA-induced dyskinesia in the MPTP-lesioned macaque model of Parkinson's disease. In: 2017 International Congress of Parkinson's Disease and Movement Disorders, Vancouver, BC, Canada, LBA 36.

Johnston, T.H., Koprich, J.B., Ravenscroft, P., Fox, S.H., Hill, M.P., Brotchie, J.M., 2013. A Battery of Motor and Non-motor Non-human Primate Behavioural Rating Scales and Tasks for Effective Translational Research in Parkinson's Disease. Society for Neuroscience, San Diego, CA, USA.

Johnston, T.H., Lane, E.L., 2011. Experimental models of l-dopa-induced dyskinesia. Int. Rev. Neurobiol. 98, 55–93.

Johnston, T.H., Lee, J., Gomez-Ramirez, J., Fox, S.H., Brotchie, J.M., 2005. A simple rodent assay for the in vivo identification of agents with potential to reduce levodopa-induced dyskinesia in Parkinson's disease. Exp. Neurol. 191, 243–250.

Johnston, T.H., van der Meij, A., Brotchie, J.M., Fox, S.H., 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.

Kalia, L.V., Lang, A.E., 2015. Parkinson's disease. Lancet 386, 896–912.

Kanda, T., Jackson, M.J., Smith, L.A., Pearce, R.K., Nakamura, J., Kase, H., Kuwana, Y., 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.

Katzenschlager, R., Manson, A.J., Evans, A., Watt, H., Lees, A.J., 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.

Kibbe, W.A., Arze, C., Felix, V., Mitraka, E., Bolton, E., Fu, G., Mungall, C.J., Binder, J.X., Malone, J., Vasant, D., Parkinson, H., Schriml, L.M., 2014. Disease Ontology 2015 update: an expanded and updated database of human diseases for linking biomedical knowledge through disease data. Nucleic Acids Res. 43, D1071–D1078.

Kieburtz, K., Landwehrmeyer, B., Reilmann, R., Savola, J.M., Eyal, E., Grachev, I., Borowsky, B., McGarry, A., Papapetropoulos, S., Hayden, M., 2017. Efficacy, Safety, and Tolerability of Pridopidine in Huntington Disease (HD): Results from the Phase II, Double-blind, Placebo-controlled, Dose-ranging Study, Pride-hd. American Academy of Neurology. Neurology, Boston, MA, USA.

Klintenberg, R., Svenningsson, P., Gunne, L., Andren, P.E., 2002. Naloxone reduces levodopa-induced dyskinesias and apomorphine-induced rotations in primate models of parkinsonism. J. Neural. Transm. 109, 1295–1307.

Ko, W.K.D., Li, Q., Cheng, L.Y., Morelli, M., Carta, M., Bezard, E., 2017. A preclinical study on the combined effects of repeated eltoprazine and preladenant treatment for alleviating L-DOPA-induced dyskinesia in Parkinson's disease. Eur. J. Pharmacol. 813, 10–16.

Kobylecki, C., Burn, D.J., Kass-Iliyya, L., Kellett, M.W., Crossman, A.R., Silverdale, M.A., 2014. Randomized clinical trial of topiramate for levodopa-induced dyskinesia in Parkinson's disease. Park. Relat. Disord. 20, 452–455.

Kobylecki, C., Hill, M.P., Crossman, A.R., Ravenscroft, P., 2011. Synergistic antidyskinetic effects of topiramate and amantadine in animal models of Parkinson's disease. Mov. Disord. 26, 2354–2363.

Kramer, M.S., Last, B., Getson, A., Reines, S.A., 1997. The effects of a selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. D4 Dopamine Antagonist Group. Arch. Gen. Psychiatr. 54, 567–572.

Kuang, Z., Thomson, J., Caldwell, M., Peissig, P., Stewart, R., Page, D., 2016. Computational drug repositioning using continuous self-controlled case series. In: The 22nd ACM SIGKDD International Conference. ACM Press, New York, New York, USA, pp. 491–500.

Kumar, S., Chowdhury, S., Kumar, S., 2017. In silico repurposing of antipsychotic drugs for Alzheimer's disease. BMC Neurosci. 1–16.
Kuzhikandathil, E.V., Bartoszyk, G.D., 2006. The novel antidyskinetic drug sarizotan elicits different functional responses at human D2-like dopamine receptors. Neuropharmacology 51, 873–884.
Lewitt, P.A., Hauser, R.A., Lu, M., Nicholas, A.P., Weiner, W., Coppard, N., Leinonen, M., Savola, J.M., 2012. Randomized clinical trial of fipamezole for dyskinesia in Parkinson disease (FJORD study). Neurology 79, 163–169.
Li, M.H., Mestre, T.A., Fox, S.H., Taati, B., 2017. Automated vision-based analysis of levodopa-induced dyskinesia with deep learning. In: Conf Proc IEEE Eng Med Biol Soc 2017. pp. 3377–3380.
Lim, S.A., Xia, R., Ding, Y., Won, L., Ray, W.J., Hitchcock, S.A., McGehee, D.S., Kang, U.J., 2015. Enhanced histamine H2 excitation of striatal cholinergic interneurons in L-DOPA-induced dyskinesia. Neurobiol. Dis. 76, 67–76.
Lopane, G., Mellone, S., Chiari, L., Cortelli, P., Calandra-Buonaura, G., Contin, M., 2015. Dyskinesia detection and monitoring by a single sensor in patients with Parkinson's disease. Mov. Disord. 30, 1267–1271.
Lundblad, M., Andersson, M., Winkler, C., Kirik, D., Wierup, N., Cenci, M.A., 2002. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. Eur. J. Neurosci. 15, 120–132.
Lundin, A., Dietrichs, E., Haghighi, S., Goller, M.L., Heiberg, A., Loutfi, G., Widner, H., Wiktorin, K., Wiklund, L., Svenningsson, A., Sonesson, C., Waters, N., Waters, S., Tedroff, J., 2010. Efficacy and safety of the dopaminergic stabilizer Pridopidine (ACR16) in patients with Huntington's disease. Clin. Neuropharmacol. 33, 260–264.
Manson, A.J., Iakovidou, E., Lees, A.J., 2000. Idazoxan is ineffective for levodopa-induced dyskinesias in Parkinson's disease. Mov. Disord. 15, 336–337.
Manson, A.J., Katzenschlager, R., Hobart, J., Lees, A.J., 2001. High dose naltrexone for dyskinesias induced by levodopa. J. Neurol. Neurosurg. Psychiatr. 70, 554–556.
Marin, C., Aguilar, E., Rodriguez-Oroz, M.C., Bartoszyk, G.D., Obeso, J.A., 2009. Local administration of sarizotan into the subthalamic nucleus attenuates levodopa-induced dyskinesias in 6-OHDA-lesioned rats. Psychopharmacology (Berlin) 204, 241–250.
Marin, C., Jimenez, A., Bonastre, M., Chase, T.N., Tolosa, E., 2000. Non-NMDA receptor-mediated mechanisms are involved in levodopa-induced motor response alterations in Parkinsonian rats. Synapse 36, 267–274.
Matz, R., Rick, W., Thompson, H., Gershon, S., 1974. Clozapine–a potential antipsychotic agent without extrapyramidal manifestations. Curr. Ther. Res. Clin. Exp. 16, 687–695.
Medicine, I. o, 2014. Drug Repurposing and Repositioning: Workshop Summary. The National Academies Press, Washington, DC.
Meekings, K.N., Williams, C.S., Arrowsmith, J.E., 2012. Orphan drug development: an economically viable strategy for biopharma R&D. Drug Discov. Today 17, 660–664.
Mestre, T.A., Beaulieu-Boire, I., Aquino, C.C., Phielipp, N., Poon, Y.Y., Lui, J.P., So, J., Fox, S.H., 2015. What is a clinically important change in the Unified Dyskinesia Rating Scale in Parkinson's disease?. Park. Relat. Disord. 21, 1349–1354.
Mestre, T.A., Johnston, T.H., Brotchie, J.M., Fox, S.H., 2010. Evolution of the ''short duration'' response to L-DOPA in the MPTP-lesioned non-human primate model of Parkinson's disease. Mov. Disord. 25, S417.
Mestre, T.A., Shah, B.B., Connolly, B.S., Aquino, C., Dhakeel, A.A., Walsh, R., Ghate, T., Lui, J.P., Fox, S.H., 2014. Famotidine, a histamine H2 receptor antagonist, does not reduce levodopa-induced dyskinesia in Parkinson's disease: a proof-of-concept study. In: Movement Disorders Clinical Practice 1, pp. 219–224.
Meyer, R.E., Mirin, S.M., Altman, J.L., 1975. The clinical usefulness of narcotic antagonists: implications of behavioral research. Am. J. Drug Alcohol Abuse 2, 417–432.
Molinari, S.P., Kaminski, R., Di Rocco, A., Yahr, M.D., 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.
Monville, C., Torres, E.M., Dunnett, S.B., 2005. Validation of the l-dopa-induced dyskinesia in the 6-OHDA model and evaluation of the effects of selective dopamine receptor agonists and antagonists. Brain Res. Bull. 68, 16–23.
Morin, N., Gregoire, L., Gomez-Mancilla, B., Gasparini, F., 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., Jourdain, V.A., Di Paolo, T., 2014. Modeling dyskinesia in animal models of Parkinson disease. Exp. Neurol. 256, 105–116.
Muller, T., Olanow, C.W., Nutt, J., Hicking, C., Laska, E., Russ, H., 2006. The PADDY-2 study: the evaluation of sarizotan for treatment-associated dyskinesia in Parkinson's disease patients. Mov. Disord. 21 (Suppl. 15), S591.
Murata, M., Odawara, T., Hasegawa, K., Iiyama, S., Nakamura, M., Tagawa, M., Kosaka, K., 2018. Adjunct zonisamide to levodopa for DLB parkinsonism: a randomized double-blind phase 2 study. Neurology 90, e664–e672.
Nadjar, A., Gerfen, C.R., Bezard, E., 2009. Priming for l-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease?. Prog. Neurobiol. 87, 1–9.
Nagarajan, M., Labrie, J.J., Regenbogen, S., Buchovecky, C.M., Pickering, C.R., Kato, L., Lisewski, A.M., Lelescu, A., Zhang, H., Boyer, S., Weber, G., Wilkins, A.D., Chen, Y., Donehower, L., Spangler, S., Lichtarge, O., Bachman, B.J., Novikov, I.B., Bao, S., Haas, P.J., Terrón-Díaz, M.E., Bhatia, S., Adikesavan, A.K., 2015. Predicting future scientific discoveries based on a networked analysis of the past literature. In: The 21th ACM SIGKDD International Conference. ACM Press, New York, New York, USA. pp. 2019–2028.
Nisbet, A.P., Foster, O.J., Kingsbury, A., Eve, D.J., Daniel, S.E., Marsden, C.D., Lees, A.J., 1995. Preproenkephalin and preprotachykinin messenger RNA expression in normal human basal ganglia and in Parkinson's disease. Neuroscience 66, 361–376.
Nosengo, N., 2016. Can you teach old drugs new tricks?. Nature 534, 314–316.
Nutt, J.G., Carter, J.H., Lea, E.S., Sexton, G.J., 2002. Evolution of the response to levodopa during the first 4 years of therapy. Ann. Neurol. 51, 686–693.
Nutt, J.G., Chung, K.A., Holford, N.H., 2010. Dyskinesia and the antiparkinsonian response always temporally coincide: a retrospective study. Neurology 74, 1191–1197.
Oh, J.D., Bibbiani, F., Chase, T.N., 2002. Quetiapine attenuates levodopa-induced motor complications in rodent and primate parkinsonian models. Exp. Neurol. 177, 557–564.
Olanow, C.W., Damier, P., Goetz, C.G., Mueller, T., Nutt, J., Rascol, O., Serbanescu, A., Deckers, F., 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.
Papa, S.M., Boldry, R.C., Engber, T.M., Kask, A.M., Chase, T.N., 1995. Reversal of levodopa-induced motor fluctuations in experimental parkinsonism by NMDA receptor blockade. Brain Res. 701, 13–18.
Papa, S.M., Chase, T.N., 1996. Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys. Ann. Neurol. 39, 574–578.
Papathanou, M., Jenner, P., Iravani, M., Jackson, M., Stockwell, K., Strang, I., Zeng, B.Y., McCreary, A.C., Rose, S., 2014. The H3 receptor agonist immepip does not affect l-dopa-induced abnormal involuntary movements in 6-OHDA-lesioned rats. Eur. J. Pharmacol. 741, 304–310.
Parkes, J.D., Baxter, R.C., Curzon, G., Knill-Jones, R.P., Knott, P.J., Marsden, C.D., Tattersall, R., Vollum, D., 1971a. Treatment of Parkinson's disease with amantadine and levodopa. A one-year study. Lancet 1, 1083–1086.
Parkes, J.D., Zilkha, K.J., Knill-Jones, R.P., Clements, P.J., Baxter, R., 1971b. L-dopa and amantadine hydrochloride in Parkinson's disease. Int. Z. Klin. Pharmakol. Ther. Toxikol. 4, 356–360.
Pearce, R.K., Jackson, M., Smith, L., Jenner, P., Marsden, C.D., 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, R.K., Smith, L.A., Jackson, M.J., Banerji, T., Scheel-Kruger, J., Jenner, P., 2002. The monoamine reuptake blocker brasofensine reverses akinesia without dyskinesia in MPTP-treated and levodopa-primed common marmosets. Mov. Disord. 17, 877–886.
Pecknold, J.C., McClure, D.J., Appeltauer, L., Wrzesinski, L., Allan, T., 1982. Treatment of anxiety using fenobam (a nonbenzodiazepine) in a double-blind standard (diazepam) placebo-controlled study. J. Clin. Psychopharmacol. 2, 129–133.
Picconi, B., Calabresi, P., 2017. Switching on the lights of dyskinesia: perspectives and limits of the optogenetic approaches. Mov. Disord. 32, 485–486.
Picconi, B., De Leonibus, E., Calabresi, P., 2018. Synaptic plasticity and levodopa-induced dyskinesia: electrophysiological and structural abnormalities. J. Neural. Transm. (Vienna)
Pierelli, F., Adipietro, A., Soldati, G., Fattapposta, F., Pozzessere, G., Scoppetta, C., 1998. Low dosage clozapine effects on L-dopa induced dyskinesias in parkinsonian patients. Acta Neurol. Scand. 97, 295–299.
Pinna, A., Ko, W.K., Costa, G., Tronci, E., Fidalgo, C., Simola, N., Li, Q., Tabrizi, M.A., Bezard, E., Carta, M., Morelli, M., 2016. Antidyskinetic effect of A2A and 5HT1A/1B receptor ligands in two animal models of Parkinson's disease. Mov. Disord. 31, 501–511.
Potts, L.F., Park, E.S., Woo, J.M., Dyavar Shetty, B.L., Singh, A., Braithwaite, S.P., Voronkov, M., Papa, S.M., Mouradian, M.M., 2015. Dual kappa-agonist/mu-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.
Quik, M., Campos, C., Grady, S.R., 2013a. Multiple CNS nicotinic receptors mediate L-dopa-induced dyskinesias: studies with parkinsonian nicotinic receptor knockout mice. Biochem. Pharmacol. 86, 1153–1162.
Quik, M., Mallela, A., Ly, J., Zhang, D., 2013b. Nicotine reduces established levodopa-induced dyskinesias in a monkey model of Parkinson's disease. Mov. Disord. 28, 1398–1406.

Rajput, A.H., Rajput, A., Lang, A.E., Kumar, R., Uitti, R.J., Galvez-Jimenez, N., 1998. New use for an old drug: amantadine benefits levodopa-induced dyskinesia. Mov. Disord. 13, 851.

Ramsperger, R., Meckler, S., Heger, T., van Uem, J., Hucker, S., Braatz, U., Graessner, H., Berg, D., Manoli, Y., Serrano, J.A., Ferreira, J.J., Hobert, M.A., Maetzler, W., team, S.-P. s, 2016. Continuous leg dyskinesia assessment in Parkinson's disease -clinical validity and ecological effect. Park. Relat. Disord. 26, 41–46.

Rascol, O., Arnulf, I., Peyro-Saint Paul, H., Brefel-Courbon, C., Vidailhet, M., Thalamas, C., Bonnet, A.M., Descombes, S., Bejjani, B., Fabre, N., Montastruc, J.L., Agid, Y., 2001. Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease. Mov. Disord. 16, 708–713.

Rascol, O., Damier, P., Goetz, C.G., Hicking, C., Hock, K., Muller, T., Olanow, C.W., Russ, H., 2006. A large phase III study to evaluate the safety and efficacy of sarizotan in the treatment of L-dopa-induced dyskinesia associated with Parkinson's disease: the Paddy-1 study. Mov. Disord. 21 (Suppl. 15), S492–S493.

Rascol, O., Fabre, N., Blin, O., Poulik, J., Sabatini, U., Senard, J.M., Ane, M., Montastruc, J.L., 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., Ferreira, J., Negre-Pages, L., Perez-Lloret, S., Lacomblez, L., Galitzky, M., Lemarie, J.C., Corvol, J.C., Brotchie, J.M., Bossi, L., 2012. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. Fundam. Clin. Pharmacol. 26, 557–564.

Rodriguez de Fonseca, F., Del Arco, I., Martin-Calderon, J.L., Gorriti, M.A., Navarro, M., 1998. Role of the endogenous cannabinoid system in the regulation of motor activity. Neurobiol. Dis. 5, 483–501.

Rudzinska, M., Bukowczan, S., Stozek, J., Zajdel, K., Mirek, E., Chwala, W., Wojcik-Pedziwiatr, M., Banaszkiewicz, K., Szczudlik, A., 2013. Causes and consequences of falls in Parkinson disease patients in a prospective study. Neurol. Neurochir. Pol. 47, 423–430.

Rylander, D., Iderberg, H., Li, Q., Dekundy, A., Zhang, J., Li, H., Baishen, R., Danysz, W., Bezard, E., Cenci, M.A., 2010. A mGluR5 antagonist under clinical development improves L-DOPA-induced dyskinesia in parkinsonian rats and monkeys. Neurobiol. Dis. 39, 352–361.

Samadi, P., Gregoire, L., Bedard, P.J., 2003. Opioid antagonists increase the dyskinetic response to dopaminergic agents in parkinsonian monkeys: interaction between dopamine and opioid systems. Neuropharmacology 45, 954–963.

Savola, J.M., Hill, M., Engstrom, M., Merivuori, H., Wurster, S., McGuire, S.G., Fox, S.H., Crossman, A.R., Brotchie, J.M., 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.

Schallert, T., Fleming, S.M., Leasure, J.L., Tillerson, J.L., Bland, S.T., 2000. CNS plasticity and assessment of forelimb sensorimotor outcome in unilateral rat models of stroke, cortical ablation, parkinsonism and spinal cord injury. Neuropharmacology 39, 777–787.

Schunack, W., 1989. Pharmacology of H2-receptor antagonists: an overview. J. Int. Med. Res. 17 (Suppl. 1), 9A–16A.

Schwab, R.S., England Jr., A.C., Poskanzer, D.C., Young, R.R., 1969. Amantadine in the treatment of Parkinson's disease. J. Am. Med. Assoc. 208, 1168–1170.

Sieradzan, K.A., Fox, S.H., Hill, M., Dick, J.P., Crossman, A.R., Brotchie, J.M., 2001. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology 57, 2108–2111.

Silverdale, M.A., Nicholson, S.L., Crossman, A.R., Brotchie, J.M., 2005. Topiramate reduces levodopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease. Mov. Disord. 20, 403–409.

Sirota, M., Dudley, J.T., Kim, J., Chiang, A.P., Morgan, A.A., Sweet-Cordero, A., Sage, J., Butte, A.J., 2011. Discovery and preclinical validation of drug indications using compendia of public gene expression data. Sci. Transl. Med. 3, 96ra77-96ra77.

Smith, C.P., Oh, J.D., Bibbiani, F., Collins, M.A., Avila, I., Chase, T.N., 2007. Tamoxifen effect on L-DOPA induced response complications in parkinsonian rats and primates. Neuropharmacology 52, 515–526.

Smith, J.L., 1985. Clinical pharmacology of famotidine. Digestion 32 (Suppl. 1), 15–23.

Smith, L.A., Jackson, M.J., Al-Barghouthy, G., Rose, S., Kuoppamaki, M., Olanow, W., Jenner, P., 2005. Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naive primates. Mov. Disord. 20, 306–314.

Spangler, S., Wilkins, A.D., Bachman, B.J., 2014. Automated hypothesis generation based on mining scientific literature. In: Proceedings of the 20th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, New York City, New York, USA. pp. 1877–1886.

Stathis, P., Konitsiotis, S., Tagaris, G., Peterson, D., 2010. Levetiracetam for the management of levodopa-induced dyskinesias in Parkinson's disease. Mov. Disord.

Stathis, P., Konitsiotis, S., Tagaris, G., Peterson, D., Group, V.-P.S., 2011. Levetiracetam for the management of levodopa-induced dyskinesias in Parkinson's disease. Mov. Disord. 26, 264–270.

Subramanian, A., Narayan, R., Corsello, S.M., Peck, D.D., Natoli, T.E., Lu, X., Gould, J., Davis, J.F., Tubelli, A.A., Asiedu, J.K., Lahr, D.L., Hirschman, J.E., Liu, Z., Donahue, M., Julian, B., Khan, M., Wadden, D., Smith, I.C., Lam, D., Liberzon, A., Toder, C., Bagul, M., Orzechowski, M., Enache, O.M., Piccioni, F., Johnson, S.A., Lyons, N.J., Berger, A.H., Shamji, A.F., Brooks, A.N., Vrcic, A., Flynn, C., Rosains, J., Takeda, D.Y., Hu, R., Davison, D., Lamb, J., Ardlie, K., Hogstrom, L., Greenside, P., Gray, N.S., Clemons, P.A., Silver, S., Wu, X., Zhao, W.-N., Read-Button, W., Wu, X., Haggarty, S.J., Ronco, L.V., Boehm, J.S., Schreiber, S.L., Doench, J.G., Bittker, J.A., Root, D.E., Wong, B., Golub, T.R., 2017. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. Cell 171, 1437–1452, e1417.

Suthram, S., Dudley, J.T., Chiang, A.P., Chen, R., Hastie, T.J., Butte, A.J., 2010. Network-based elucidation of human disease similarities reveals common functional modules enriched for pluripotent drug targets. PLoS Comput. Biol. 6, e1000662.

Svenningsson, P., Rosenblad, C., Af Edholm Arvidsson, K., Wictorin, K., Keywood, C., Shankar, B., Lowe, D.A., Bjorklund, A., Widner, H., 2015. Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study. Brain 138, 963–973.

Thomas, A., Iacono, D., Luciano, A.L., Armellino, K., Di Iorio, A., Onofrj, M., 2004. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 75, 141–143.

Tronci, E., Fidalgo, C., Stancampiano, R., Carta, M., 2015. Effect of selective and non-selective serotonin receptor activation on L-DOPA-induced therapeutic efficacy and dyskinesia in parkinsonian rats. Behav. Brain Res. 292, 300–304.

Tronci, E., Fidalgo, C., Zianni, E., Collu, M., Stancampiano, R., Morelli, M., Gardoni, F., Carta, M., 2014. Effect of memantine on L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease. Neuroscience 265, 245–252.

Ungerstedt, U., 1971. Postsynaptic supersensitivity after 6-hydroxy-dopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol. Scand. Suppl. 367, 69–93.

Ungerstedt, U., Arbuthnott, G.W., 1970. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. Brain Res. 24, 485–493.

Vanunu, O., Magger, O., Ruppin, E., Shlomi, T., Sharan, R., 2010. Associating genes and protein complexes with disease via network propagation. PLoS Comput. Biol. 6, e1000641–1000649.

Varanese, S., Howard, J., Di Rocco, A., 2010. NMDA antagonist memantine improves levodopa-induced dyskinesias and "on-off" phenomena in Parkinson's disease. Mov. Disord. 25, 508–510.

Verhagen Metman, L., Del Dotto, P., Blanchet, P.J., van den Munckhof, P., Chase, T.N., 1998a. Blockade of glutamatergic transmission as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Amino Acids 14, 75–82.

Verhagen Metman, L., Del Dotto, P., Natte, R., van den Munckhof, P., Chase, T.N., 1998b. Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. Neurology 51, 203–206.

Verhagen Metman, L., Del Dotto, P., van den Munckhof, P., Fang, J., Mouradian, M.M., Chase, T.N., 1998c. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology 50, 1323–1326.

Verhoeven, W.M., Tuinier, S., Sijben, N.A., van den Berg, Y.W., de Witte-van der Schoot, E.P., Pepplinkhuizen, L., van Nieuwenhuizen, O., 1992. Eltoprazine in mentally retarded self-injuring patients. Lancet 340, 1037–1038.

Vidal, E.I., Fukushima, F.B., Valle, A.P., Villas Boas, P.J., 2013. Unexpected improvement in levodopa-induced dyskinesia and on-off phenomena after introduction of memantine for treatment of Parkinson's disease dementia. J. Am. Geriatr. Soc. 61, 170–172.

Visanji, N.P., Fox, S.H., Johnston, T., Reyes, G., Millan, M.J., Brotchie, J.M., 2009. Dopamine D3 receptor stimulation underlies the development of L-DOPA-induced dyskinesia in animal models of Parkinson's disease. Neurobiol. Dis. 35, 184–192.

Vizuete, M.L., Traiffort, E., Bouthenet, M.L., Ruat, M., Souil, E., Tardivel-Lacombe, J., Schwartz, J.C., 1997. Detailed mapping of the histamine H2 receptor and its gene transcripts in Guinea-pig brain. Neuroscience 80, 321–343.

Wang, Y., Wang, H.S., Wang, T., Huang, C., Liu, J., 2014. L-DOPA-induced dyskinesia in a rat model of Parkinson's disease is associated with the fluctuational release of norepinephrine in the sensorimotor striatum. J. Neurosci. Res. 92, 1733–1745.

Ward, H.W., 1973. Anti-oestrogen therapy for breast cancer: a trial of tamoxifen at two dose levels. Br. Med. J. 1, 13–14.

West, R.J., Jarvis, M.J., Russell, M.A., Carruthers, M.E., Feyerabend, C., 1984. Effect of nicotine replacement on the cigarette withdrawal syndrome. Br. J. Addict. 79, 215–219.

Wetzel, H., Szegedi, A., Hain, C., Wiesner, J., Schlegel, S., Benkert, O., 1995. Seroquel (ICI 204 636), a putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters. Psychopharmacology (Berlin) 119, 231–238.

Wichmann, T., DeLong, M.R., 2003. Pathophysiology of Parkinson's disease: the MPTP primate model of the human disorder. Ann. N. Y. Acad. Sci. 991, 199–213.

Wijtmans, M., Leurs, R., de Esch, I., 2007. Histamine H3 receptor ligands break ground in a remarkable plethora of therapeutic areas. Expet Opin. Invest. Drugs 16, 967–985.

Wolz, M., Lohle, M., Strecker, K., Schwanebeck, U., Schneider, C., Reichmann, H., Grahlert, X., Schwarz, J., Storch, A., 2010. Levetiracetam for levodopa-induced dyskinesia in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. J. Neural. Transm. 117, 1279–1286.

Wong, K.K., Alty, J.E., Goy, A.G., Raghav, S., Reutens, D.C., Kempster, P.A., 2011. A randomized, double-blind, placebo-controlled trial of levetiracetam for dyskinesia in Parkinson's disease. Mov. Disord. 26, 1552–1555.

Wu, H., Huang, J., Zhong, Y., Huang, Q., 2017. DrugSig: a resource for computational drug repositioning utilizing gene expression signatures. PLoS One 12, e0177743–0177711.

Zhang, D., McGregor, M., Bordia, T., Perez, X.A., McIntosh, J.M., Decker, M.W., Quik, M., 2015. alpha7 nicotinic receptor agonists reduce levodopa-induced dyskinesias with severe nigrostriatal damage. Mov. Disord. 30, 1901–1911.

Zhang, P., Agarwal, P., Obradovic, Z., 2013. Computational drug repositioning by ranking and integrating multiple data sources. In: Machine Learning and Knowledge.

Zhang, P., Wang, F., Hu, J., 2014. Towards drug repositioning: a unified computational framework for integrating multiple aspects of drug similarity and disease similarity. In: AMIA… Annual Symposium Proceedings/AMIA Symposium. AMIA Symposium 2014. pp. 1258–1267.