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Drugs of abuse and Parkinson's disease

Leah R. Mursaleen [a,b,c], Jonathan A. Stamford [a,b,*]

[a] The Cure Parkinson's Trust, 120 Baker Street, London W1U 6TU, United Kingdom
[b] Parkinson's Movement, 120 Baker Street, London W1U 6TU, United Kingdom
[c] The University of Sussex, Life Sciences, Brighton BN1 9RH, United Kingdom

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ABSTRACT

The term "drug of abuse" is highly contextual. What constitutes a drug of abuse for one population of patients does not for another. It is therefore important to examine the needs of the patient population to properly assess the status of drugs of abuse. The focus of this article is on the bidirectional relationship between patients and drug abuse. In this paper we will introduce the dopaminergic systems of the brain in Parkinson's and the influence of antiparkinsonian drugs upon them before discussing this synergy of condition and medication as fertile ground for drug abuse. We will then examine the relationship between drugs of abuse and Parkinson's, both beneficial and deleterious. In summary we will draw the different strands together and speculate on the future merit of current drugs of abuse as treatments for Parkinson's disease.

1. Dopamine

Dopamine (3,4-dihydroxyphenylethylamine), perhaps more than any other neurotransmitter, is responsible for controlling not only our ability to move and interact with our environment, but also our reasons for doing so. Dopamine regulates our emotion and drive. It alters our perception of reward and punishment. It reinforces behavioural circuits and acts to choose individual behavioural components. This allows us to feel pleasure and drives us to seek more. Dopamine is the means and the motive for our behaviour, both appropriate and aberrant (Baik, 2013).

Despite this wide neuronal brief, much of this functionality is achieved through two principal projections ascending from adjacent cell clusters in the mesencephalon. The nigrostriatal pathway sends axons from the substantia nigra pars compacta (A9 cell group) to the corpus striatum, comprised of the caudate nucleus and putamen, separated by the internal capsule (Roeper, 2013). The mesocorticolimbic pathway, originating in the ventral tegmental area of Tsai (A10 cell group) projects principally to the nucleus accumbens and frontal cortex, via the mesolimbic and mesocortical subdivisions (Le Moal, 2000). The two pathways both ascend in a single topographically mapped nerve trunk, the median forebrain bundle, to their telencephalic targets.

Although inevitably a gross oversimplification, the work of the nigrostriatal pathway can, in broad terms, be thought of as the planning, initiation and expression of movement (Matsumoto et al, 1999). Dopaminergic dysregulation in the mesocortical targets is involved in the symptomatology of schizophrenia (Abi-Dargham & Moore, 2003) while altered dopaminergic function in the mesolimbic pathway is pivotally implicated in the pathogenesis and neuropsychopharmacology of addiction (Di Chiara & Imperato, 1988).

2. The role of dopamine in the pathology of Parkinson's

Although, since Braak's hypothesis, there is much debate about the wider (especially preclinical) pathology of Parkinson's (Braak et al., 2003), there is little doubt that damage to the nigrostriatal pathway in general, and to the dopaminergic cells of the substantia nigra particularly, accounts for much of the motor pathology of Parkinson's. This has been demonstrated extensively over the last 50 years, in human and animal studies, culminating in the award of the 2000 Nobel Prize to Arvid Carlsson for his discovery of dopamine as a neurotransmitter. Selective lesions of the nigrostriatal pathway in animals by neurotoxins or surgical ablation mimic many of the gross neurological features of Parkinson's (Simola et al., 2007). Similar features can be engendered by drugs or genetic modifications which reduce catecholamine storage (Fernandes et al., 2012; Patel et al., 2003). Moreover drugs such as the neuroleptics, which block dopamine receptors can produce parkinsonian states in both animals and man (Bohlega & Al-Foghom, 2013). Post-mortem studies in man confirm extensive nigral dopamine cell loss in patients with Parkinson's (Jellinger, 1999).

Abbreviations: L, Dopa (levedopa); MAO, inhibitors (monoamine oxidase B); COMPT, inhibitors (catechol-o-methyl transferase); MPTP, (1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine); MPPP, (1-Methyl-4-phenyl-4-propionoxypiperidine); MPDP, (1-Methyl-4-phenyl-1, 2-dihydroxypyridinium ion); MDMA, (3, 4-methylenedioxy-methamphetamine); ROS, (reactive oxygen species); A2A, (adenosine 2A); 6-OHDA, (6-hydroxydopamine); CB1, (type 1 cannabinoid receptor); 5-HT, (5-Hydroxytryptamine or serotonin).

* Corresponding author at: The Cure Parkinson's Trust, 120 Baker Street, London W1U 6TU, United Kingdom. Tel.: +44 207 487 3892.
E-mail address: jon.stamford@parkinsonsmovement.com (J.A. Stamford).

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3. The clinical presentation of Parkinson's

The diagnosis of Parkinson's is made clinically by a neurologist, largely on the basis of motor symptoms. In 1817 James Parkinson identified three key neurological findings as central to what he called *paralysis agitans* or the shaking palsy (Parkinson, 1817). These were tremor, rigidity and bradykinesia, and although not present in all cases, these remain the cardinal signs of Parkinson's, along with postural instability, used for diagnostic purposes. But the key point here is that diagnosis is made on the basis of motor rather than non-motor symptoms. Increasingly however, the non-motor symptoms of Parkinson's (loss of sense of smell, depression, anxiety, pain, bladder and bowel problems, panic attacks et cetera) are being recognised as key parts of the overall symptomatology (Chen et al., 2013). Indeed, so widespread and disparate are the symptoms, that it is appropriate to think of Parkinson's less as a movement disorder than as a complex progressive neuropsychiatric condition and this is enforcing a rethink on the clinical definition of Parkinson's (Berg et al., 2014).

In many respects, the medical community's tardiness in recognising the importance of non-motor symptoms has perhaps reflected the relative lack of consensus on pharmacological management of non-motor symptoms (Connolly & Lang, 2014).

4. Role of dopamine in the treatment of Parkinson's

Just as nigrostriatal dopamine loss accounts for the key motor manifestations of Parkinson's, so it also forms the basis of virtually all contemporary pharmacotherapy. In essence the therapeutic target in Parkinson's is to replace the dopamine lost by neurodegeneration and ensured that the post-synaptic dopamine receptors are activated in as near to normal a manner as possible (Bibbiani et al., 2005). Treatments therefore broadly fall into one of two categories — boosting levels of dopamine in the terminal fields, or replacement of dopamine by exogenous agonists. L-Dopa, the historical mainstay of treatment, boosts dopamine levels by conversion to dopamine although it should be said that some of this conversion takes place in non-dopaminergic neurons such as serotonin terminals (Lopez et al., 2001). Monoamine oxidase B (MAO-B) inhibitors, such as selegiline or rasagiline, and catechol-o-methyl transferase (COMT) inhibitors such as entacapone and tolcapone are mostly adjuncts to L-dopa (Marin & Obeso, 2010). The dopamine D2 class agonists, such as rotigotine, ropinirole and pramipexole aim to replace dopamine in the biophase and stimulate the post-synaptic dopamine receptors, in a manner largely independent of endogenous neuronal activity.

Bearing in mind the symptomatic value of L-dopa in enhancing synaptic dopamine levels, one might anticipate that dopamine uptake inhibitors would have a use in Parkinson's. Yet, as a class, these have been therapeutic failures. With the exception of benztropine, used primarily for its anticholinergic properties (Brocks, 1999), none have joined the antiparkinsonian armoury. The problem here is not so much an inability to elevate extracellular dopamine as its control. Many of the classical dopamine uptake inhibitors also have the capacity to release dopamine from intracellular stores (Stamford et al., 1986, 1989). In consequence many of these dopamine uptake inhibitors — such as cocaine and amphetamine — are known drugs of abuse (Vaughan & Foster, 2013). Amphetamine has shown some benefit (Parkes et al., 1975) although the authors were quick to concede that striatal dopamine loss might limit its effectiveness. Nomifensine, a mixed dopamine and noradrenaline uptake inhibitor was used for a while as an antidepressant but, was of negligible use in Parkinson's (Bedard et al., 1977). That said, another catecholamine uptake inhibitor, methylphenidate, has recently shown promise in some aspects of Parkinson's, particularly freezing (Delval et al., 2014) so it may be time to revisit this class of drugs.

5. Role of dopamine in treatment side effects

None of the above drugs have any regional specificity. Although the main therapeutic benefit relates to their actions in the nigrostriatal pathway, none of the drugs are specifically targeted to that location. Where there are dopamine receptors, they will be activated by dopamine agonists. Where there are dopamine neurons, they will respond to L-dopa by increasing dopamine release. It is this non-specificity that, in a large part, accounts for many of the more problematic adverse events seen in Parkinson's. Although stimulation of post-synaptic receptors in the caudate nucleus and putamen is beneficial in Parkinson's, activation of the same receptors in the nucleus accumbens and frontal cortex is considerably less welcome.

Common side effects of dopaminergic therapy in Parkinson's include vivid dreams, REM sleep behavioural disorder, auditory, visual and olfactory hallucinations, impulse control disorders, pathological gambling, hypersexuality, behavioural stereotypy and internet addiction (Zhang et al., 2014). These effects appear to be particularly prominent with the dopamine agonists (Moore et al., 2014) and the effects of this drug class are widely reported in the lay literature.

6. The role of the limbic dopamine systems

To those working in the field of addiction, the behavioural patterns found in many patients following antiparkinsonian medication, are characteristic of drugs of abuse. Drugs that raise dopamine levels or post-synaptic dopaminergic tone in the nucleus accumbens in particular have a high psychogenic propensity and addictive potential (Espana & Jones, 2013).

The mesolimbic neuronal tract represents the key reward pathway in the brain. Activation of dopamine release, or post-synaptic dopamine stimulation, in the nucleus accumbens is a key feature both of drugs and behavioural patterns that are rewarding. Whether a pleasurable activity or a tablet of amphetamine, the actions are similar (Di Chiara et al., 1993). Indeed addictive drugs from widely differing pharmacological classes act in a similar way on the mesolimbic dopamine system, to the extent that this pathway is considered the final common route of expression for addictive drugs and hedonic behaviour (Pierce & Kumaresan, 2006). The link between mesolimbic dopamine and creativity is also well established and many Parkinson's patients experience bouts of creativity correlated with increases in dopaminergic stimulation (Faust-Socher et al., 2014; Lhommée et al., 2014)

7. Parkinson's personalities

It has been suggested for many years that there is a characteristic behavioural phenotype for Parkinson's patients — meek, gentle and passive (Menza, 2000). However with the evolution of the condition and the apparent increase in young onset Parkinson's (<40 years), this is clearly an oversimplification. Behaviourally the young onset patients are quite different (Schrag et al., 2003). These different behavioural profiles inevitably call for different pharmacological management and it requires careful judgement on behalf of the neurologist to match treatment to persona (Callesen et al., 2014).

In a recent series of informal polls conducted on the Parkinson's Movement Community of Health Unlocked (https://healthunlocked.com/parkinsonsmovement), we examined attitudes of the Parkinson's community to recreational drugs. In response to the question "*Do you believe there is a role for recreational drugs in the treatment of Parkinson's?*", more than half of the respondents answered positively (see Fig. 1). Only 8.3% felt there was "probably not" or "definitely not" a role. Of course many recreational drugs are illegal and this may be a significant barrier to their usage. We therefore asked patients whether they sometimes took more of their Parkinson's medication than prescribed if it made them feel good. Although the majority answered "never", around one in 10 patients answered "sometimes" or "frequently" (see Fig. 2). We also asked, as a crude measure of drug abuse, whether the patients used

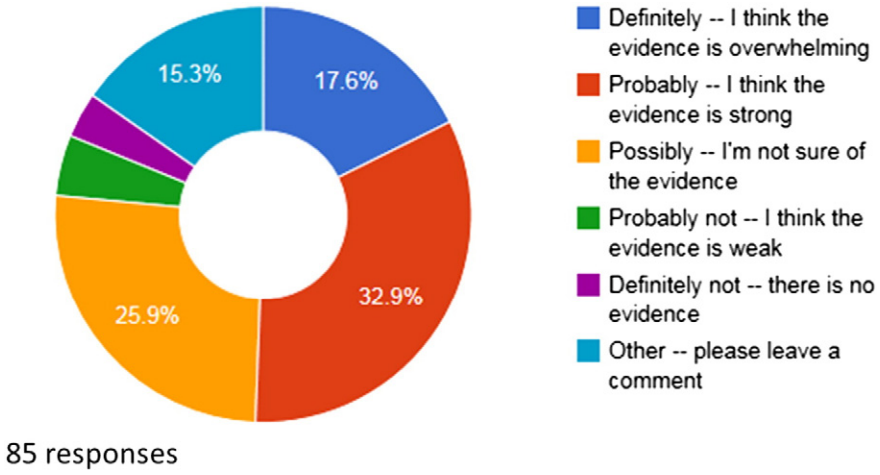

Fig. 1. Do you believe there is a role for recreational drugs in the treatment of Parkinson's?

recreational cannabis. We divided the responses according to whether the patients were prescribed solely dopamine agonists, solely L-dopa or a combination of both. The number of respondents was low in each group but the proportions who used recreational cannabis "very often" were higher in the dopamine agonist group (23.1%) than in the L-dopa or the combination group (11.4% and 10.7% respectively: see Fig. 3). When asked about the barriers to a wider use of recreational drugs in Parkinson's, the "illegal status" of the drugs was identified as the most common barrier, along with "unproven efficacy" and "concerns over long-term safety" (see Fig. 4).

8. Drugs of abuse and Parkinson's — cause or effect?

In the treatment of a long-term illness such as Parkinson's, it is not always easy to distinguish what is disease-related from iatrogenic causes. Evidently however, whatever the cause, many Parkinson's patients are amenable to pharmacological solutions outside the pharmacopoeia.

The literature on drugs of abuse and Parkinson's falls broadly into two categories — those in which the drug may be causally related to Parkinson's and those in which a given drug of abuse may show some therapeutic benefit. It goes without saying that there are few randomised controlled trials of illegal drugs in Parkinson's.

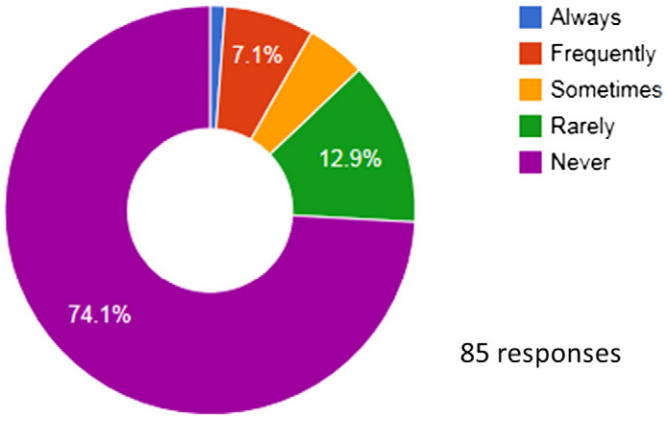

Fig. 2. Do you take more of your Parkinson's medication than prescribed because it makes you feel good?

9. Drugs of abuse as causes of Parkinson's

9.1. Synthetic heroin, sloppy chemistry and MPTP

Many drugs have been implicated in neurotoxicity particularly within the dopamine pathways affected in Parkinson's. Therefore some drugs of abuse are thought to possibly be causative of Parkinson's and this is particularly evident with MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine). In 1982, several individuals in the region of San Francisco developed a Parkinson-like disorder following intravenous administration of MPTP an accidental by-product of incompetent synthesis of the synthetic heroin 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) (Gupta, 2011). Mixtures with varying amounts of MPPP and MPTP were sold as heroin in the San Francisco Bay area which resulted in many individuals with symptoms of bradykinesia, rigidity, tremor, flexed posture, loss of postural reflexes, and drooling following intravenous administration of MPTP (Langston and Ballard, 1985), symptoms redolent of classical Parkinson's.

While a personal tragedy for those addicts accidentally poisoned, the wealth of clinical data led to an upsurge of interest in the mechanisms of Parkinson's. MPTP was a new tool and the results of inadvertent MPTP use in humans demonstrate that abuse of this compound closely reproduces the symptomatology of idiopathic Parkinson's (Gupta, 2011). MPTP is not neurotoxic itself, the associated neurotoxicity comes from the formation of the metabolite MPP^+ through a biotransformation process (Schmidt & Ferger, 2001) via conversion to 1-methyl-4-phenyl-1, 2-dihydroxypyridinium ion (MPDP) by MAO-B (Chiba et al., 1984; Markey et al., 1984) which is spontaneously oxidised to form MPP^+ (Schmidt & Ferger, 2001). Via the plasma membrane dopamine transporter (DAT), dopaminergic nerve terminals take up MPP^+ (Chiba et al., 1985; Javitch et al., 1985) which is expressed on nerve terminals and dendrites (Schmidt & Ferger, 2001), which suggests that MPTP toxicity targets the striatum and the substantia nigra. This is supported by findings in non-human primates treated with MPTP which resulted in a decreased release of dopamine in the striatum, dopamine accumulation causing swollen axons in the nigrostriatal pathway (Burns et al., 1983; Burns et al., 1985), followed by extensive loss of nerve cells in the pars compacta of the substantia nigra (Langston et al., 1984), and a marked reduction in the dopamine contents of the striatum (Schmidt & Ferger, 2001).

9.2. Psychostimulants and neurotoxicity

The psychostimulants (amphetamine, cocaine etc.) have potent effects on forebrain dopamine release (Espana & Jones, 2013; Stamford et al., 1986), making them widespread drugs of abuse. More recently there has been an accumulation of evidence also suggesting a causative

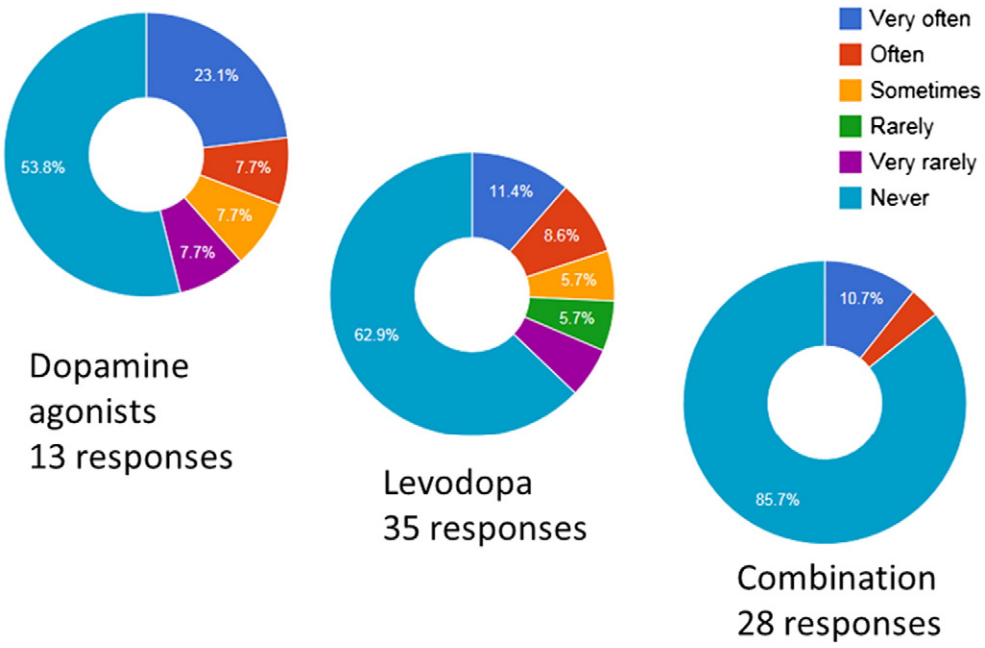

Fig. 3. Do you use recreational cannabis?

effect of stimulant abuse, particularly involving the psychostimulant methamphetamine, in the development of Parkinson's (Thrash et al., 2009). A study on the long-term effects of stimulant use (methamphetamine, cocaine and MDMA) suggests that there is an abnormal substantia nigra morphology exhibited in individuals with a history of illicit stimulant use, a major risk factor for developing Parkinson's in later life (Todd et al., 2013). Moreover, methamphetamine and MDMA (3,4-methylenedioxy-methamphetamine) can increase lipid peroxidation and DNA oxidation as well as elevating levels of reactive oxygen species (ROS) such as hydroxyl and hydrogen peroxide (Granado et al., 2013). Oxidative stress to lipids and DNA of the cells within the target pathways results in neurotoxicity (Cadet & Brannock, 1998; Yamamoto and Zhu, 1998), specifically selective striatal nerve terminal damage (Granado et al., 2008, 2010; Thomas et al., 2004) and loss of dopamine in the nucleus accumbens (Granado et al., 2008, 2010). At high concentrations methamphetamine can act as a monoamine oxidase inhibitor (Thrash et al., 2009) and as dopamine metabolism generates ROS it is highly likely that oxidative stress, which can occur immediately after methamphetamine administration, facilitates neuronal toxicity (Yamamoto and Zhu, 1998).

9.3. Methamphetamine

Methamphetamine is the stimulant that has been most closely linked with the development of Parkinson's; compared to healthy controls,

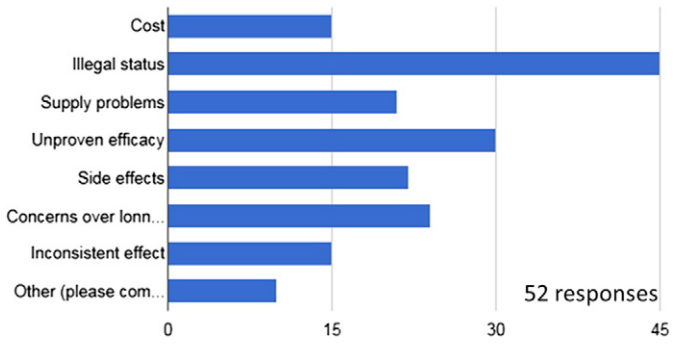

FIg. 4. What are the barriers to wider use of recreational drugs for Parkinson's?

people with a history of methamphetamine abuse are 1.76 times more likely to develop Parkinson's later in life (Callaghan et al., 2012). Methamphetamine easily crosses the blood–brain barrier, triggering the release of monoamines (dopamine, noradrenaline and serotonin) via an immediate signalling cascade (Thrash et al., 2009). It also acts as a reuptake inhibitor for dopamine and noradrenaline prolonging activity at the synapse (Krasnova & Cadet, 2009). It is this excessive increase in synaptic dopamine induced by methamphetamine which is linked to its neuropathology (Krasnova & Cadet, 2009). Methamphetamine particularly stimulates the mesolimbic reward and nigrostriatal pathways, prohedonic actions which lead people to commonly abuse the drug (Thrash et al., 2009).

High doses and chronic low dose administration of methamphetamine produce losses in many markers of central dopaminergic and serotoninergic neurons even after 2–3 years of abstinence, these include reduction of the concentrations of dopamine and serotonin and their uptake sites as well as a reduction in precursor enzyme activities (tyrosine and tryptophan hydroxylase) and the transporter levels (McCann et al., 2012; Thrash et al., 2009; Volkow et al., 2001) as well as reductions in striatal blood flow (Chung et al., 2010). These neurochemical modifications translate into neurological sequelae — detoxified methamphetamine users perform poorly on motor skill tests to a similar level as people with Parkinson's (McNeely et al., 2012). This is supported by evidence from rodent models where retrograde and progressive nigrostriatal damage similar to Parkinson's pathology was observed in rats' post-mortem after 28 days and 56 days of abstinence (Kousik et al., 2014). This long-lasting damage is likely to add to the reported higher risk for later developing Parkinson's (Callaghan et al., 2012). However, very recent data on the amphetamines not only confirms prior observations but, if anything, implicates methamphetamine even more clearly as a risk factor for Parkinson's (Curtin et al., 2015).

9.4. Cocaine

The literature on neurodegeneration and cocaine usage is a little more ambiguous. In post-mortem and in vivo human studies cocaine use has been found to diminish striatal and mesencephalic dopamine neuronal markers which suggests that in humans cocaine use likely causes a loss of dopamine neurons (Little et al., 2009), predisposing individuals to neurodegeneration like Parkinson's. Previous rodent studies however did not detect this dopamine cell damage with cocaine

administration (Little et al., 2009) and it was previously thought that cocaine did not cause the characteristic neurodegeneration of other drugs of abuse that interact with brain dopamine pathways (Ryan et al., 1988). For example Ryan et al.(1988) found degeneration of frontal granular cortex and neostriatum in rodents who administrated dexamphetamine over three days but no degeneration in these areas with administration of cocaine over the same time period. Interestingly, more recent data provided by Callaghan et al. (2012) seems to support findings from previous rodent studies, showing a lack of increase in risk of a subsequent diagnosis of Parkinson's in hospitalised cocaine users but a massive increase in the risk of subsequent diagnosis of Parkinson's in methamphetamine and other amphetamine-type stimulant users.

10. Drugs of abuse in the treatment of Parkinson's

Although some drugs of abuse are closely linked with the pathology and development of Parkinson's, this is not universal. In many epidemiologic studies other addictive behaviours such as cigarette smoking and coffee drinking, have been linked with a lower risk of idiopathic Parkinson's (Hernán et al., 2002). For example, cigarette smokers have a 60% lower risk of developing Parkinson's compared to people who have never smoked and coffee drinkers have a 30% lower risk of developing the disease compared to non-coffee drinkers (Hernán et al., 2002). This suggests that some drugs of abuse are actually neuroprotective against Parkinson's and other evidence (see below) even suggests that some drugs of abuse could be used in the treatment of Parkinson's, in the elevation of symptoms and side effects of medication as well as perhaps even a reduction in the progression of neurodegeneration.

10.1. Nicotine

The reduction in susceptibility to Parkinson's is a well-documented effect of cigarette smoking which suggests a pharmacological action of some compound in cigarette smoke against nigral neuronal damage (Alves et al., 2004; Greenbaum et al., 2013). Specifically, nicotine seems to have a neuroprotective effect against dopaminergic damage; in the striatum of mice and non-human primates nicotine has been reported to protect against parkinsonian MPTP damage (Quik et al., 2007b) as well as to improve motor function in animal models of Parkinson's (Meshul et al., 2002).

Since many genetic variants within the gene cluster (CHRNA5–CHRNA3–CHRNB4) for the nicotinic cholinergic receptor seem to be associated with nicotine dependence associated with smoking, Greenbaum et al. (2013) investigated whether among smokers these genetic variants are linked with age at onset of Parkinson's. Three independent single nucleotide polymorphisms within the gene cluster (rs588765, rs16969968, rs578776) were analysed for any relationship with age of onset. Greenbaum et al. (2013) found that the nicotine dependent risk variant rs588765 seems to have a protective effect in Parkinson's and is associated with later age of onset. However this was only the case for individuals who have been exposed to nicotine (current smokers or previous smokers), not in individuals who had never smoked (Greenbaum et al., 2013). It has therefore been hypothesised that a slower rate of disease progression should also be seen with cigarette smoking in patients already diagnosed with Parkinson's (Alves et al., 2004). However from a study over an 8 year period Alves et al. (2004) found that there were no significant differences in the development of parkinsonism, cognitive impairment and mood in smoking and non-smoking patients with Parkinson's and that mortality rate was also similar in the two groups. This lack of influence on the progression of Parkinson's seems to indicate that nicotine does not have a particular neuroprotective effect in diagnosed patients and therefore it is unlikely to be useful in halting or slowing the progression of Parkinson's. That said, there is some evidence for beneficial effects of nicotine with regard to the motor symptoms of Parkinson's as well as in reducing L-dopa induced dyskinesia (Kalia et al., 2013). The results from a pilot trial administrating chronic high-dose nicotine via patches to people with Parkinson's found improvements in motor symptoms in advanced Parkinson's (Villafane et al., 2007). What's more, nicotine has been found to reduce dyskinesia in L-dopa treated rodents (Bordia et al., 2008) and primates (Quik et al., 2007a) and there is now oral nicotinic receptor agonists being developed to treat L-dopa induced dyskinesia (Kalia et al., 2013) suggesting a very real possibility for nicotine in the treatment of Parkinson's.

10.2. Caffeine

There is compelling evidence that caffeine intake is associated with reduced risk of developing Parkinson's in many epidemiological studies (Meissner et al., 2011; Prediger, 2010). This inverse relationship is present with tea as well as with coffee and is not present with decaffeinated coffee, which appears to confirm that the effect is specifically due to caffeine and not the drinks themselves (Ascherio and Chen, 2003; Tan et al., 2007). Caffeine is a non-specific adenosine receptor antagonist which acts on A1 and A2 receptors (Meissner et al., 2011). The principal mechanisms of action relevant to Parkinson's are its antagonism of the adenosine 2A (A2A) G-protein-coupled receptor involved in the activity of the indirect dopamine pathway (Postuma et al., 2012). A2A receptors have selective basal ganglia expression with particularly high concentration in the striatum in humans and rodents and convergent epidemiological and laboratory data suggest that blockade of A2A receptors in the striatum may be neuroprotective against the underlying dopaminergic neurodegeneration of Parkinson's (Xu et al., 2005). The potential use of A2A antagonism in the treatment of Parkinson's, with the likes of caffeine, has also been proposed from preclinical evidence that suggests a link between A2A antagonism and both disease modification and symptomatic relief (Xu et al., 2005).

Early clinical studies found no effect of caffeine as a symptomatic agent and have also failed to show any positive effect of A2A antagonism on disease progression, however these were small-scale and limited with regard to dosing and assessment (Simon et al., 2008). More recent studies have documented improvements in the symptoms of Parkinson's with a daily intake of caffeine for example in gait ataxia and freezing (with 100 mg daily) (Kitagawa et al., 2007). In a recent randomised controlled trial Postuma et al. (2012) reported improvement in motor symptoms with caffeine intake. What's more, post-mortem analysis of Parkinson's patients has found that, in the patients who experienced dyskinesia, there was increased striatal A2A receptor expression and binding particularly in the putamen compared to the patients who had not and the control group (Calon et al., 2004; Martinez-Mir et al., 1991). This is also supported by evidence from animal studies where L-dopa-treated unlesioned monkeys have shown increased levels of A2A mRNA (Zeng et al., 2000). This has also been observed in 6-hydroxydopamine (6-OHDA) lesioned rats treated with L-dopa (Tomiyama et al., 2004) and no changes of striatal A2A gene expression in 6-OHDA-lesioned animals have been seen in those not treated with L-dopa or any other Parkinson's medication (Kaelin-Lang et al., 2000; Martinez-Mir et al., 1991). This evident increased expression of A2A in the striatopallidal pathway with the development of dyskinesia strongly suggests that increased adenosinergic transmission through A2A receptors plays a pivotal role in L-dopa-induced dyskinesia (Xu et al., 2005). From this a clear possible use of caffeine in the treatment of Parkinson's is evident, using caffeine for blockade of striatal A2A receptors decreasing adenosinergic transmission to possibly alleviate dyskinetic symptoms of L-dopa use in people with Parkinson's.

10.3. Alcohol

In epidemiologic studies, the association of alcohol consumption with a lower risk of Parkinson's is neither as strong nor consistent as with nicotine and caffeine (Hernán et al., 2003). When the incidence of Parkinson's between alcoholics and non-alcoholics in the General

Practice Research Database of the United Kingdom were compared, a lower incidence of Parkinson's among alcoholics compared with non-alcoholics was not found (Hernán et al., 2004). Moreover the risk of Parkinson's has also been found to be similar in individuals who usually consume moderate amounts of alcohol and in abstainers (Hernán et al., 2003). However, Eriksson et al. (2013) studied the association between diagnosed alcohol use disorders and Parkinson's using Swedish subjects from 1972–2008, and found that a history of an alcohol use disorder did in fact confer an increased risk of admission to hospital with a Parkinson's diagnosis in both women and men but the risk did seem to be higher when the age of first admission was lower. This would seem to suggest that alcohol abuse in general is potentially neurotoxic increasing the likelihood of diagnosis of Parkinson's.

Conversely, red wine is known to have antioxidant properties (Okawara et al., 2007). Resveratrol, a red wine polyphenol, is thought to be where the therapeutic antioxidant properties of red wine reside (Blanchet et al., 2008). As the dopamine neurodegeneration seen in Parkinson's is likely to be in part due to oxidative stress (Jenner, 2003; Reynolds et al., 2007), it has been hypothesised that this molecule in red wine might be neuroprotective against Parkinson's. Evidence for this theory comes from MPTP-lesioned mice (Blanchet et al., 2008): daily administration of resveratrol prevented the depletion of striatal dopamine associated with MPTP administration and resulted in more abundant TH-immunopositive neurons than in mice only given MPTP (Blanchet et al., 2008).

10.4. Cannabinoids

Cannabis, a cannabinoid receptor agonist, is another potential drug of abuse recently implicated in the pharmacotherapy of many medical conditions but particularly Parkinson's. Animal data strongly supports a role for cannabinoids in motor control, due to the high density of cannabinoid receptors in the basal ganglia (Giuffrida & McMahon, 2010; Howlett et al., 2002). For instance, the highest density of CB1 receptors in the body are found in the globus pallidus and substantia nigra pars reticulate (Sanudo-Pena et al., 1999) and compared to other brain regions the concentration of the endocannabinoid anandamide in these areas is three times higher (Di Marzo et al., 2000). Further, there is colocation of CB1 and D1/D2 receptors in striatal neurons (Hermann et al., 2002) and it has been found that lower locomotor activity is exhibited by CB1 knockout (Lynn and Herkenham, 1994) confirming that the basal ganglia control of movement also involves the cannabinoid system (Giuffrida & McMahon, 2010).

That said, the potential use of cannabinoids to treat Parkinson's is controversial. The potential utility of both cannabinoid agonists and antagonists has been evaluated in many studies of which have produced conflicting results, particularly when comparing rodent and primate models (Cao et al., 2007; Mesnage et al., 2004; Papa, 2008; van der Stelt et al., 2005). There is however general agreement that the basal ganglia in Parkinson's has an overactive endocannabinoid system (Brotchie, 2003). Both CB1 receptor agonists and antagonists seem to have therapeutic potential, both in Parkinson's and L-dopa induced dyskinesia (Pacher et al., 2006). When focused on the external segment of the global pallidus (GPe) enhanced CB1 receptor signalling can also enhance GABA transmission, leading to inhibition of dopamine activity in the GPe and thereby contribution to parkinsonian symptoms (Pacher et al., 2006). CB1 receptor antagonists, therefore, if targeted to attenuate CB1 signalling in the GPe may be useful for alleviating the bradykinesia of Parkinson's (Pacher et al., 2006). However if in the striatum the enhanced CB1 receptor signalling is an attempt of the parkinsonian brain to normalise striatal function, amplification of this signalling with a CB1 agonist such as cannabis might alleviate symptoms of Parkinson's (Gerdeman and Lovinger, 2001; Gubellini et al., 2002).

Experimental evidence on the development of L-dopa induced dyskinesia suggests a deficiency in endocannabinoid transmission (Venderová et al., 2004). Several reports have also shown that activation of CB1 receptors reduce L-dopa induced dyskinesias (Ferrer et al., 2003; Morgese et al., 2007) and therefore this effect of cannabinoid agonists may occur through modulating glutamatergic input from cortico-striatal neurons (Gerdeman et al., 2002; Gubellini et al., 2002) and perhaps increasing synaptic plasticity mediated by endocannabinoids in the striatum, which in 6-OHDA-treated rats are both dysfunctional (Kreitzer and Malenka, 2007).

Treatment with CB1 receptor agonists has the capacity to protect against dopaminergic cell death, decrease tremor and improve motor impairment (Lastres-Becker et al., 2005). Although it would seem that the use for reducing bradykinesia is unlikely due to their hypokinetic profile seen in both humans and primates (Brotchie, 2003; Croxford), evidence from questionnaires show cannabis used to alleviate bradykinesia, muscle rigidity and tremor (Venderová et al., 2004). This unusual effect on bradykinesia is possible due to over activity of endocannabinoid transmission being associated with nigrostriatal dopaminergic dysfunction in the basal ganglia (Pacher et al., 2006).

From questionnaires most patients only report improvements after about 2 months of using cannabis and suggest that long-term regular use of cannabis is important in order to gain beneficial effects of it on Parkinson's symptoms (Venderová et al., 2004). That said, Sieradzan et al. (2001) found beneficial that synthetic cannabinoid agonist action occurs within minutes to hours after administration. Therefore synthetic cannabinoids could be useful for the fast treatment of the symptoms of Parkinson's as well as to reduce L-dopa induced dyskinesia.

10.5. MDMA

Much has been written about MDMA and Parkinson's. MDMA, a non-specific serotonergic agent has been reported to reduce dyskinesia in Parkinson's patients taking L-dopa, potentially to a level where normal function is restored (Fox et al., 2006; Johnston et al., 2012; Morton, 2005) and also normalise motor activity in the MPTP-lesioned marmoset (Fox et al., 2006). This is controversial because the development of Parkinson's has also been linked to MDMA abuse (Todd et al., 2013) and therefore the possibility of using it in the treatment of the dyskinesias associated with the L-dopa treatment of Parkinson's (Nutt et al., 2013) is difficult to comprehend. Similar to the reported effects of caffeine, controlled experiments have shown that MDMA not only reduces dyskinesia but also the dose of L-dopa needed to control the symptoms of Parkinson's (Morton, 2005) which would thereby further reduce the likely incidence of dyskinesia. This supports earlier findings in animal studies that MDMA improves dyskinesia in L-dopa medicated monkey models of Parkinson's (Iravani et al., 2003). Recent evidence from animal models suggest that the dysregulation of serotonin (5-hydroxytryptamine or 5-HT) is involved in these dyskinesias, and therefore it is likely that the dyskinesia-reducing effect of MDMA as well as the evidence of MDMA normalising motor symptoms in MPTP- lesioned marmosets (Fox et al., 2006) and in rats with haloperidol-induced Parkinsonism (Schmidt et al., 2002) is due to its enhancement of 5-HT levels (Huot et al., 2011).

In a study on MDMA-assisted psychotherapy for women with chronic post-traumatic stress disorder, Bouso et al. (2008) found that for all subjects' low single dose administration of MDMA between 50 and 75 mg were safe both psychologically and physiologically. Therefore it seems that at low doses MDMA could potentially be used as a therapeutic, however this is not to suggest that MDMA should be administered to people with Parkinson's as a treatment because not only is the safety of long-term administration undetermined due to the use of single dosing here but also because political pressures led to the early closing of this study which resulted in only 6 subjects to be treated (Bouso et al., 2008). Therefore at present MDMA does not represent a viable therapeutic candidate due both to its psychogenic properties such as hallucinations and depression which are often already heightened in Parkinson's patients especially those on dopamine agonists (Johnston et al., 2012; Morton, 2005), as well as its well-characterised potential for neurotoxicity seen with lifetime usage (Johnston et al., 2012; Parrott, 2014). Instead, potential

analogues of MDMA should be turned to as a treatment of Parkinson's (Johnston et al., 2012) due to the difficulties in completing clinical trials using MDMA.

11. Conclusions

Although it goes without saying that there are few randomised controlled trials of illegal drugs in Parkinson's, it seems as though cannabinoids and MDMA as well as caffeine and nicotine (not illegal but drugs of abuse nonetheless), all have some real therapeutic potential for Parkinson's disease, particularly with reducing L-dopa induced dyskinesia but also possibly in improving the movement deficits of Parkinson's itself, both of which warrant further research. That said, the purpose of this article was not to simply make the case for drugs of abuse in a general sense, but to demonstrate also that there is a unique symbiosis between patient and drug. In other words, the condition itself determines what constitutes a drug of abuse. Parkinson's and its prescribed treatments all have direct effects on the reward pathways in the brain. As such, and in that context, the prescribed medicines themselves can be thought of as drugs of abuse.

Drug abuse in Parkinson's most likely reflects an overall hedonia predisposing the patient to abuse not only the classical drugs of abuse but also their own prescribed medicines. It is important to take into account the importance of patient personality in the development of addiction. Nowhere is this more important than in Parkinson's.

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