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Review

Methamphetamine use and future risk for Parkinson's disease: Evidence and clinical implications

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ABSTRACT

Background: Methamphetamine use has been posited to be a risk factor for the development of Parkinson's disease (PD) and parkinsonism. The clinical implications of a potential association between methamphetamine use and PD are considered.

Methods: A review of methamphetamine and PD and parkinsonism was conducted, including evidence from animal models, clinical and population studies.

Results: There is biological plausibility to a link between methamphetamine use and PD. Though clinical and epidemiological evidence in this area is scant, a number of studies suggest that methamphetamine is associated with a moderately increased risk of PD and parkinsonism, and may also lead to premature onset of PD. The long lag time between exposure to methamphetamine and onset of PD, the potential for recovery from neurotoxic effects, and tobacco smoking each may attenuate the association. Individual and drug use characteristics that may modulate a user's risk remain poorly understood.

Conclusions: The use of methamphetamine may be an initiating event in the development of PD and parkinsonism, in addition to other risk factors that a given individual may hold. Clinicians should be vigilant to signs of prodromal and emerging PD among methamphetamine users. In individuals with premature onset illness, information on current or prior exposure to methamphetamine should be sought.

1. Introduction

Methamphetamine use is a significant public health problem, with an estimated 35 million stimulant users worldwide, predominantly of methamphetamine (Degenhardt and Hall, 2012; Degenhardt et al., 2013; UNODC, 2016). Harmful physical and mental health consequences are common, including cardiovascular and cerebrovascular pathology, psychosis, suicide and premature mortality (Callaghan et al., 2012a; Darke et al., 2008, 2011; Karch, 2015). The stimulants methamphetamine and its active metabolite amphetamine are highly related and are hereafter referred to as methamphetamine (McKetin et al., 2016)

There has been recent speculation that methamphetamine use may be associated with greater risk of developing Parkinson's disease (PD). Here, we examine the question whether methamphetamine users are at increased risk of PD or parkinsonism. There is an extensive pre-clinical literature investigating the effects of methamphetamine on brain tissue, and specifically its propensity to cause brain dopamine neuronal damage such as that observed in Parkinson's disease. This literature has been comprehensively reviewed elsewhere (Kish et al., 2017). The current review extends beyond these preclinical findings by reviewing evidence from clinical and population studies of PD and parkinsonism among individuals exposed to methamphetamine. The clinical implications for methamphetamine users, their communities and clinicians are considered.

1.1. Pathology of Parkinson's disease and parkinsonism

PD is characterized by the clinical manifestations of bradykinesia in combination with rest tremor and/or rigidity (Postuma et al., 2015), and by the underlying pathology of irreversible loss of dopamine in the basal ganglia (or striatum) of the brain. Dopaminergic cell loss occurs following degeneration of dopaminergic neurons in the substantia nigra (Kish et al., 2017). The characteristic motor symptoms that prompt diagnosis present at a relatively late stage in the pathological process. The term parkinsonism is distinct, and refers only to the clinical motor manifestations (bradykinesia, tremor, rigidity) (Postuma et al., 2015), that is, not specifying the underlying cause. These features may be

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attributable to PD or to other causes. That parkinsonism therefore comprises a broader category than PD is reflected in illness prevalence; the lifetime risk of parkinsonism is estimated at 4.4% for men and 3.7% for women (Elbaz et al., 2002), while that of PD is estimated at 2% for men and 1.3% for women (Elbaz et al., 2002).

PD is rare before the age of fifty (Twelves et al., 2003), but increasingly common with age (Poewe et al., 2017). The prevalence in those aged 65 and older is in the order of 2–3% (Poewe et al., 2017). Approximately 10% of cases have an identifiable genetic cause (Ascherio and Schwarzschild, 2016). In the remainder, referred to as 'idiopathic' PD, the pathogenic mechanisms are poorly understood.

Selective striatal dopamine deficiency is the hallmark feature of PD, together with the widespread accumulation of intracellular protein (α-synuclein) in intracellular inclusions known as Lewy bodies (Poewe et al., 2017). Over recent decades, however, it has become clear that PD pathogenesis is not limited to the dopaminergic system, but rather involves numerous cell types in both the central and the peripheral autonomic nervous systems (Poewe et al., 2017). Lewy pathology is observed early in both cholinergic and monoaminergic neurons in the brainstem and in olfactory system neurons, and more latterly, with disease progression, in the limbic system and neocortex (Poewe et al., 2017). A range of mechanisms and pathways have been implicated, including α-synuclein proteostasis, calcium homeostasis, oxidative stress, mitochondrial function, axonal transport, and neuroinflammation (Poewe et al., 2017). It appears that both behavioural and environmental effects modify the risk (Ascherio and Schwarzschild, 2016).

Drug-induced parkinsonism is the second most common aetiology of parkinsonism after idiopathic PD (López-Sendón et al., 2013). Drug-induced parkinsonism, relating to prescribed drug treatments, is a side effect most commonly associated with antipsychotic agents, but which can occur with a variety of other treatments including antidepressants, calcium channel antagonists, antiarrhythmic and antiepileptic drugs (López-Sendón et al., 2013). There is evidence that at least some of these drugs may cause neurotoxic damage to nigrostriatal dopaminergic neurons (Mena et al., 1995). Despite being considered reversible on drug discontinuation, suspected drug-induced parkinsonism renders as many as 25% of individuals subject to progressive or persisting parkinsonism (Marti Masso and Poza, 1996).

2. Evidence from preclinical and human studies

2.1. Evidence from preclinical studies: is there a plausible mechanism?

Striatal dopamine nerve terminal markers, including the dopamine metabolite, homovanillic acid, the striatal dopamine transporter, and the vesicular monoamine transporters (VMAT) are all observed at low levels in PD, indicating the hallmark deficiency of the dopaminergic system (Kish et al., 2017). The rate of dopaminergic neuronal loss is initially exponential: a study of neuronal loss in PD brains compared to that in ageing brains demonstrated 45% neuronal loss during the first decade of PD, ten times that accounted for by ageing (Fearnley and Lees, 1991). In some regions of the substantia nigra, average neuronal loss in PD exceeded 90% (Fearnley and Lees, 1991).

Methamphetamine and its metabolite amphetamine cause release of dopamine from dopaminergic neurons in the human brain (Laruelle et al., 1995). Evidence from animal studies using both histological techniques and dopamine marker measurement indicates that methamphetamine exposure induces structural damage in dopaminergic neurons (reviewed in Kish et al., 2017). Repeated, high-dose methamphetamine administration modifies the dopamine transporter, a possible mechanism in long-lasting dopaminergic deficits (Fricks-Gleason et al., 2016). In animal studies, dopamine synthesis may recover within six months of amphetamine exposure, indicating that at least some dopaminergic effects are reversible (Melega et al., 2008).

2.2. Evidence from human studies: is there a plausible mechanism?

Evidence from human studies is limited. There are reduced levels of striatal dopamine (Moszczynska et al., 2004; Wilson et al., 1996) and of dopamine markers, such as the dopamine transporter (McCann et al., 1998, 2008; Volkow et al., 2001a). Striatal dopamine levels reduced by up to 50% have been observed in chronic methamphetamine users (Wilson et al., 1996). Moszczynska et al. (2004) conducted one of very few studies examining, at autopsy, the basal ganglia of human chronic methamphetamine users. The study found prominent reductions in dopamine levels, which were greater in the caudate nucleus (61%), than the putamen (50%). This pattern differed to that observed in PD controls, in whom mean dopamine levels were more marked in the putamen (loss of 97%) than in the caudate (loss of 82%). The putamen and caudate are entailed in motor and cognitive function respectively, and it was posited that dopamine reduction in the caudate may explain cognitive impairment in some methamphetamine users, and that the relative sparing of the putamen might explain the absence of PD. There was considerable variability in the levels of dopamine loss observed. While several exhibited very severe dopaminergic deficiency, the authors concluded that, in the majority, the doses used recreationally would not give rise to significant irreversible damage to dopaminergic neurons (Kish et al., 2017). This was a small sample (n = 20), however, and there were no pre-mortem clinical characteristics reported. Of note, the methamphetamine users in the sample had a median age of 31 years with a modal 10 years' duration of use. It is unknown how many may have progressed to PD had they lived longer.

2.3. Evidence from preclinical studies: are the neurotoxic effects of methamphetamine irreversible?

The risk for PD increases with age, with continued progressive loss of dopaminergic neuronal integrity. If methamphetamine-related effects on dopaminergic neuronal integrity were chronic and irreversible, the baseline for dopaminergic function would be lower than in non-methamphetamine users. Thus, it is plausible that with progressive age-related loss of dopaminergic function, methamphetamine users will achieve prematurely the threshold of dopamine function loss required for clinical manifestation of parkinsonism. This prompts the question: does the observed dopaminergic neuronal integrity damage induced by methamphetamine use constitute permanent degenerative change or reversible modulatory effects?

Neuronal degeneration in animals is observed at high methamphetamine doses that exceed those of recreational use in humans (Woolverton et al., 1989), and thus may not be a good preclinical model of human methamphetamine abuse. There is insufficient evidence to answer the question whether recreational methamphetamine use in humans causes such irreversible loss of dopaminergic neurons (Kish et al., 2017). Binge-like dosing is more deleterious in animal models, with more severe or longer-lasting effects than comparable cumulative dosing over time (Moszczynska and Callan, 2017). Of note, prior methamphetamine exposure attenuates the later binge-induced striatal dopamine level decrease, perhaps indicative of tolerance to the neurotoxic effects of methamphetamine (McFadden et al., 2015). Nonetheless, evidence for a strong dose-dependent relationship between amphetamine use and neural toxicity has been demonstrated in a variety of animal species, including rodents and primates (Yamamoto et al., 2010).

2.4. Evidence from human studies: are the neurotoxic effects of methamphetamine irreversible?

Evidence from the neurocognitive literature is pertinent here. Reviews suggest that methamphetamine abuse is associated with mild cognitive impairment (Dean et al., 2013), which, in turn, is associated with effects on dopamine function (Volkow et al., 2001b). Importantly,

suppression of cognitive abilities improves with abstinence from methamphetamine, at least in some individuals (Dean et al., 2013; Kim et al., 2006; Salo et al., 2009; Scott et al., 2007). Further, the observed improvement in function following abstinence, at least in some cognitive domains such as memory and executive function, is associated with partial recovery in methamphetamine related neuronal integrity (Chou et al., 2007; Dean et al., 2013). Recovery may, however, not be complete, as some cognitive impairments persist in abstinent methamphetamine users and correlate with markers of decreased dopaminergic neuronal integrity (McCann et al., 2008). There are caveats to the interpretation of these neurocognitive findings, such as whether neurocognitive deficits occur in all individuals, and whether the differences observed are clinically significant (Hart et al., 2012). Nonetheless, evidence from animal and human studies suggests that there is damage to dopaminergic neurons in methamphetamine users, that these changes in dopaminergic neuronal integrity show some potential to recover with abstinence, and that recovery is associated with improvement in (cognitive) function.

While neurocognitive effects are observable at the time of current methamphetamine use, the PD paradigm is different: abnormalities in striatal dopaminergic neurons will only give rise to the clinical manifestations of parkinsonism when the required 50% threshold loss of dopaminergic function is met. That the acute catastrophic development of parkinsonism is not observed in young methamphetamine users indicates that this level of damage does not result acutely. It may be the case however, as is speculated in neurocognition, that there is some irreversible damage to neurons, with a resultant depletion of dopaminergic neurons. Such neuronal depletion will not be detectable at the time. This is important because, unlike in neurocognition, it is not possible to study the gradual development of PD in neuroimaging or human studies. Rather, the illness may develop after a variable lag time post-exposure to methamphetamine and will present with clinical motor features at a late stage in the disease process.

3. Evidence from population and clinical studies

Population and clinical studies provide a means of examining whether individuals exposed to methamphetamine have an increased prevalence for PD or parkinsonism. In a large population sample, Callaghan et al. (2012b) reported that individuals admitted to hospital with methamphetamine-use disorders had a 76% increased risk of developing PD over 16-year follow-up compared to a matched population-proxy appendicitis group. Curtin et al. (2015), in a retrospective cohort study of hospitalizations and outpatient service use among methamphetamine users and controls, reported a 3.1 times increased risk of PD in users. These findings support Callaghan et al. (2012b), and indicate that an increased risk for future development of PD is not limited to those with use severe enough to warrant hospital admission. Indeed, a limitation of hospital population-based datasets is that there may be underestimation of exposure to methamphetamine use, and of PD, for which hospital admission is not (yet) indicated. Another important difference between these studies was the more inclusive definition of PD/parkinsonism/essential tremor employed by Curtin et al. (2015). They did, however, confirm an increased risk of 2.8 times controls in methamphetamine users when applying the more stringent PD only diagnosis.

While these two population studies provided evidence of increased risk for PD among methamphetamine users, it remained a rare event. This warrants discussion. It has been argued that only a subset of individuals may be susceptible to developing PD (Callaghan et al., 2012b), though there is a lack of evidence about which individual and/or drug use characteristics increase risk. Studies to date have not examined mode of administration, dosing, duration of use, or duration of abstinence, so it is unclear to what extent these factors impact risk. Reduced risk for PD is associated with tobacco smoking (Chen et al., 2010). The high rates of nicotine smoking among methamphetamine users may somewhat underestimate the risk conferred by methamphetamine (Callaghan et al., 2012b; Curtin et al., 2015). High mortality among methamphetamine users prevents many reaching an age at which PD might otherwise become diagnosable (Darke et al., 2017).

Stimulant drugs including amphetamine have, for decades, been used in the treatment of other conditions including narcolepsy and attention deficit hyperactivity disorder (ADHD). Clinical studies of the long-term effects of stimulant exposure in ADHD have not been conducted (Huang and Tsai, 2011). A study among patients with PD found narcolepsy to be an additional morbidity much more commonly present than would be expected in the general population (Christine et al., 2012). Exposure to amphetamines (for the treatment of narcolepsy) was found to occur at a rate five times higher than that expected among those with PD, raising the question whether amphetamines accounted for this increased risk of comorbid narcolepsy and PD (Christine et al., 2012). This lends support to the proposal that there is under-detection of an association between methamphetamine and PD. This finding only came to light because there is appropriate recording of amphetamine exposure as a treatment prescribed for narcolepsy in patient medical records. In other settings, information on illicit substance use may be neither sought nor provided.

Finally, Garwood et al. (2006) found that individuals with PD were eight times more likely than their carers to have had prior prolonged exposure to prescribed, or illicit, amphetamine use. The average exposure occurred 27 years before diagnosis. Overall, population studies report a two- to three-fold increased risk of development of PD and parkinsonism among chronic users (Callaghan et al., 2012b; Curtin et al., 2015), and several studies suggest an increased risk in individuals exposed to prescribed or illicit amphetamines.

3.1. Evidence from experimental studies in human methamphetamine users

To date, studies have been based on large-scale populations from clinical sources that document diagnosed syndromes. There is a lack of evidence regarding the prevalence of subthreshold or threshold parkinsonian features among non-clinical populations of chronic MA users.

Various movement disorders associated with methamphetamine use have been described, both acute hyperkinetic presentations such as chorea and tics, and more persistent effects such as psychomotor disturbances and parkinsonism (Caligiuri and Buitenhuys, 2005). Chronic motor effects exist in human methamphetamine users, such as deficits in fine dexterity and timed gait tasks (Volkow et al., 2001b). These effects were observed in users who had been abstinent for at least 12 months, indicating that some psychomotor changes endure. Whether these movement disorders are associated with increased risk of future development of PD or parkinsonism is unclear. It is unclear whether the effects observed in the methamphetamine users were irreversible or due to neurotoxicity. Indeed, it has been argued that such psychomotor disturbances may reflect deficits in higher-order cognitive functions such as planning, attention, and/or executive function (Simon et al., 2000). This conclusion is consonant with the findings of Moszczynska et al. (2004) (discussed in Section 2.1) that methamphetamine-related neurotoxic effects were more pronounced in the striatal areas implicated in cognitive function than those involved in motor function.

While it is not possible to measure dopaminergic integrity itself in living individuals, an important potential marker is that of abnormal substantia nigra (SN) pathology. SN hyperechogeneity can be demonstrated in between 80 and 90% of living adults with PD using transcranial sonography (Berg et al., 2001; Tsai et al., 2007). SN hyperechogeneity in healthy adult humans is associated with presynaptic dopaminergic dysfunction (Berg et al., 2001). It is also highly predictive of future development of PD: affected older (50 years+) adults were shown to be 17 times more likely to develop PD within 3 years than those without the abnormality (Berg et al., 2011). A larger area of SN hyperechogeneity was observed in living adults with a history of illicit amphetamine (predominantly methamphetamine) use compared to

controls in a case-control study (Todd et al., 2016). The amphetamine users also showed some features of parkinsonism, scoring significantly more highly than controls on a clinical rating scale for PD. Deficits were noted particularly in movement domains such as hand movements and movement speed, speech, posture and postural stability (Todd et al., 2016). There was no correlation between the area of SN hyperechogeneity and duration of abstinence (mean = 3.6 years), leading the authors to conclude that the abnormality was likely to be long-lasting. Indeed, SN hyperechogeneity appears to be an irreversible risk factor for PD, as there have been no reported cases of improvement in any population once the abnormality has been detected (Todd et al., 2016).

The two studies detailed above demonstrate that it is possible that subtle parkinsonian features are present in methamphetamine users. It is likely that subthreshold or indeed threshold symptoms and signs may go undetected and, thus, untreated among methamphetamine users who demonstrate reduced help-seeking behaviours (McKetin and Kelly, 2007).

4. What modulatory factors might impact on the association between methamphetamine and Parkinson's disease?

Individual and drug use factors may influence the degree to which a methamphetamine user experiences neurotoxic effects or subsequent recovery. Age of onset and cessation may be important, as neural plasticity and brain reserve may explain the ability of younger individuals to experience better outcomes following neurological injury (Hukkelhoven et al., 2003; Satz et al., 2011). There is much still to learn about the degree to which irreversibility of neuronal integrity is, or is not, impacted by duration of exposure to methamphetamine use, route of administration, dependence, or form (e.g., low-potency prescribed psychostimulants through to high-potency crystalline methamphetamine).

Dose and duration of exposure effects, too, are poorly understood. The available data relate to cognitive impairment, rather than PD. Cumulative methamphetamine exposure has not been associated with degree of cognitive impairment in most studies (Dean et al., 2013). This is, perhaps, not surprising, given that the observed cognitive impairment is mild. Thus, in the early phases of methamphetamine use, there would be expected to be some association with a degree of impairment, but once that mild impairment has been established it is likely that ongoing use is associated with a plateauing in impairment. Thus, further ongoing exposure over time would not be associated with further impairment. Duration of illness *per se* may thus not be the best measure of methamphetamine dose effects. Parkinsonian features may occur more frequently among individuals with binge-use patterns, based on animal models that binge-like dosing is more deleterious (Moszczynska and Callan, 2017). Measures of addiction severity similarly yield mixed findings: dependence was found to be associated with poorer cognitive performance in some (McKetin and Mattick, 1997) but not all studies (Hoffman et al., 2006).

Smoking of nicotine may be an important modulator of the association between methamphetamine use and parkinsonism, as nicotine reduces the risk of PD (Chen et al., 2010). Smoking is very common among methamphetamine users, with a prevalence of 95% in dependent users (McKetin et al., 2012). This is many times higher than the general population prevalence of smoking of between 10 and 20 percent reported in the U.S. and Australia where most population and clinical studies have been conducted (AIHW, 2017; CDC, 2016). In animal models, nicotine has been shown to be neuroprotective, attenuating MA-induced nigrostriatal damage and altering nicotinic acetylcholine receptor expression (Baladi et al., 2016; Vieira-Brock et al., 2015). Thus, smoking nicotine may attenuate MA-induced neurotoxic effects and reduce the likelihood of later development of parkinsonism.

Potential individual-level modulators include male gender, Hispanic ethnicity, exposure to neurotoxins, comorbid physical illness such as HIV (associated with parkinsonism-like symptoms) or psychiatric illnesses and their treatments (Langston et al., 1987; Tse et al., 2004; Van Den Eeden et al., 2003). Several case reports of drug-induced PD/parkinsonism have been reported in men aged below 45 years treated on antipsychotic treatment who were also taking prescribed or illicit amphetamines (Matthew and Gedzior, 2015; Tcheremissine and Englert, 2013). Genetic profile is increasingly investigated when considering the pathogenesis of various subtypes of PD (Thenganatt and Jankovic, 2014). Polymorphism in the genes involved in dopamine regulation and detoxification may modulate an individual's susceptibility to PD (Singh et al., 2008). Thus, genetic variability in the metabolism of methamphetamine leading to potential neurotoxic effects (Cherner et al., 2010) may be relevant to a methamphetamine user's future risk of development of PD. Genetic susceptibility among individuals from families with familial PD is evidenced by high rates of drug-induced parkinsonism (Hoenicka et al., 2002). The issue of genetic profile as a modulator of the association between methamphetamine use and PD is an area for future study. Additionally, models of the pathogenesis of PD continue to evolve: disease mechanisms at both molecular and cellular levels are increasingly implicated, such as progressive development of Lewy body pathology (Poewe et al., 2017). Thus, it is possible that nigrostriatal dopaminergic loss associated with methamphetamine use alone is not sufficient to entail the development of PD. Other, as yet unspecified, pathogenetic mechanisms may be additionally required.

Finally, methamphetamine administration can much more rarely lead to acute onset of persistent parkinsonism following vascular ischaemic damage to the basal ganglia (Deeb et al., 2017; Tang et al., 2017), with methamphetamine associated with an increased risk of stroke (Lappin et al., 2017). Cases occurring by this alternative mechanism are rare and would not be expected to share the same risk factors as discussed above for progressive PD secondary to nigrostriatal dopaminergic neuronal loss.

5. Is methamphetamine associated with premature development of Parkinson's disease?

When considering the chronic development of PD, it is important to consider exposure to risk factors over time. An analogy can be drawn with the now well-recognised association between methamphetamine exposure and increased risk for hypertension and cardiovascular disease (Darke et al., 2017). Current use of methamphetamine would not be expected to necessarily confer risk for chronic cardiovascular disease. Rather, chronic exposure confers a cumulative risk which, in addition to other risk factors in an individual, gives rise to accelerated ageing. Cardiovascular pathology among chronic methamphetamine users is comparable to that observed in individuals decades older (Huang et al., 2016; Karch, 2015; Kaye et al., 2007). This leads to the question whether similar methamphetamine-associated accelerated ageing effects may be relevant to PD?

There is some evidence from population studies for the premature development of PD. Callaghan et al. (2012b) found that the median age of onset of PD was six years younger among methamphetamine users than controls. Comparisons of onset age of PD in methamphetamine users compared to controls were not reported by Curtin et al. (2015), but the age of PD onset was early, with a median age around 45 years. One small clinical study compared patients with prolonged amphetamine exposure with unexposed PD controls, and found a younger onset age in the amphetamine-exposed group, with no difference in clinical features (Christine et al., 2010).

It is noteworthy that the risk for later development of PD is *not* common to all psychostimulants. Both Callaghan et al. (2012b) and Curtin et al. (2015) included hospitalized cocaine users as comparison groups in their studies of later diagnosis of PD. Both found there to be no increased risk in the cocaine user groups (Callaghan et al., 2012b; Curtin et al., 2015). These findings are consistent with evidence from animal studies that cocaine exposure is not associated with the

neurodegeneration effects observed with amphetamine (Ryan et al., 1988).

Finally, it is worthy of note that, to date, only a small number of clinical and epidemiological studies have been conducted on this important issue. Methamphetamine users are delayed in help-seeking across a range of conditions (McKetin and Kelly, 2007), so it is plausible that individuals currently or previously exposed to methamphetamine have symptoms of PD and parkinsonism that have never been detected or diagnosed. Further studies across a range of clinical populations are needed to explore the association of methamphetamine and risk for PD and parkinsonism.

6. Clinical implications

Onset of PD is rare before age 60, and very rare before 50 (Van Den Eeden et al., 2003). Manifestations of PD or parkinsonism in younger people, therefore, should be treated with concern and a detailed history of prior exposure to methamphetamine and/or other prescribed and illicit substances should be sought. Individual risk factors as discussed above should be identified. Premature onset of PD at any age may warrant enquiry about current or prior methamphetamine use. It is important to document the use patterns and time course of methamphetamine exposure, and to note smoking history.

Clinicians caring for methamphetamine users should be vigilant in examining for the characteristic motor symptoms of PD and for the less well-known prodromal symptoms of constipation, reduced sense of smell, and sleep disorders which may precede the onset of motor symptoms by up to twenty years (Savica et al., 2010). Where indicated, screening for parkinsonian motor features with sensitive instruments of motor function should be conducted, designed to detect subthreshold parkinsonian features among current or previous methamphetamine users.

Many individuals experience symptoms of PD for years before their diagnosis is recorded (Ascherio and Schwarzschild, 2016), and may benefit from a range of both pharmacological (dopamine agonists, levodopa, monoamine oxidase-B inhibitors) and non-pharmacological treatments, such as occupational therapy, speech and language therapy, and deep brain stimulation (Rogers et al., 2017). There is no evidence to date regarding the effectiveness of such treatments in individuals who have developed Parkinson's disease associated with methamphetamine use. It is also unknown whether such individuals may be more, or less, likely to develop adverse side effects such as impulse control disorders (compulsive eating, spending, gambling, or sexual behaviour) that are associated with dopamine agonist treatment in PD (Weintraub et al., 2010).

Methamphetamine users seeking medical assistance with a range of conditions may be more susceptible to drug-induced parkinsonism; therefore, there should be preference for selection of drugs less likely to cause this. For example, in the treatment of psychosis where there is current or prior methamphetamine use, preference should be given to antipsychotic agents that are associated with low rates of drug-induced parkinsonism, such as quetiapine (López-Sendón et al., 2013).

Current high rates of methamphetamine use may herald significant future health burden from PD for hospital and community health services for years to come. The potential future risk of PD and parkinsonism should be highlighted to people who may use or have formerly used methamphetamine and to their communities in order to ensure appropriate help seeking, detection, and intervention. An intervention to be encouraged in the primary prevention of PD is the promotion of physical activity, which may be neuroprotective (Ascherio and Schwarzschild, 2016). Finally, where methamphetamine use is indicated in the development of PD, there may be implications for optimal management of both PD and methamphetamine maintenance treatment.

7. Conclusions

In summary, over twenty years of research in animals and humans have established a biological plausibility to an association between methamphetamine exposure and PD and parkinsonism. In contrast to the many preclinical studies in this area, to date only a handful of clinical and epidemiological studies have investigated this important issue. Further studies across a range of clinical populations are needed to explore the association of methamphetamine and risk for PD and parkinsonism throughout adult life. There is evidence from a variety of sources of a link between methamphetamine use and the development of PD and parkinsonism. While we must be cautious, the use of methamphetamine may be an initiating event in the development of Parkinson's disease and parkinsonism, in addition to other risk factors that a given individual may hold.

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Conflict of interest

No conflict declared by any of the authors.

Contributors

Authors Lappin, Darke and Farrell conceptualized the study. Authors Lappin and Darke conducted the data collection, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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