Parkinson’s Disease and Drug Abuse

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Abstract

Background: Parkinson’s disease is described as hypokinetic symptoms with cardinal features such as tremors, bradykinesia, gait difficulties as well as cognitive problems. Much research has been done with regards to drugs of abuse such as opiates, amphetamines, cocaine as well as therapeutic drugs causing this disease.

Objectives: To provide a brief literature review in context to different reports with Parkinson’s and drug abuse and understand the implications of drugs on basal ganglia circuitry.

Methods: I present different reports collected of different drug interactions along with their studies, in an attempt to assimilate all the results and come to a conclusion.

Results: Use of drugs such as heroin, Methcathinone, inhalants, amphetamines, cocaine as well as therapeutic drugs such as prokinetic and SSRIs may predispose persons to Parkinson’s disease though NSAIDs have no such association.

Conclusions: Effect of such drugs in causing Parkinson’s should be discussed with patients on a clinical basis especially in the context of drug abuse.

Keywords: Parkinson’s; Drugs of Abuse

Introduction

Parkinson’s Disease (PD) is a multisystem neurodegenerative disorder which is characterized by loss of dopaminergic neurons in the midbrain which leads to characteristic symptoms of slowing of movement, muscular rigidity and resting tremor [1]. Parkinsonism is defined by the same clinical features as seen in Parkinson’s Disease but entails as separate form of pathophysiology as seen in diffuse Lewy body disease, multiple system atrophy, progressive supranuclear palsy, encephalitis, brain injury, Wilsons disease, brain damage caused by anaesthesia drugs (such as during surgery), carbon monoxide poisoning, mercury poisoning and other chemical poisonings, overdoses of narcotics, MPTP (a contaminant in some street drugs) [2].

Common symptoms include: Decrease in facial expressions, difficulty starting and controlling movement, Soft voice, Stiffness of the trunk, arms, or legs, tremor, mental confusion and memory loss leading to dementia. Several drugs have been implicated in secondary parkinsonism. These usually include antipsychotics, antiemetics, antidopaminergics.

Here we shall discuss the correlation between drug abuse and Parkinson’s disease by first delving into the pathophysiology of the disease, correlating the mechanism of drug action with the addiction circuit and reviewing the overall interaction of the drugs that lead to the development of Parkinson’s disease.

Pathophysiology of Parkinsonism and addiction pathway

The Basal Ganglia consists of an organized group of nuclei which include the Caudate, Putamen, Globus Pallidus, Subthalamic Nucleus (STN), and Substantia Nigra are located deep to the cortex that surround the Thalamus and are superior to the brainstem. They process the information received to coordinate movement. It consists of 4 main pathway or loops, these are Motor, Oculomotor, Prefrontal, and Limbic loop, the loops relevant to motor functions are motor and oculomotor loop.

The primary motor, premotor (lateral premotor and supplementary motor) and Somatosensory cortices to the Striatum, in particular the Putamen, sends input to the motor loop, this input then returns back to the Motor region through the Ventral Anterior (VA) and Ventral Lateral (VL) nuclei of the Thalamus after it has been thoroughly processed.

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The Posterior Parietal cortex and Prefrontal cortex transfer input signals to the oculomotor loop which it sends to the body of the Caudate in the Striatum. After processed the signal is sent back to the Frontal Eye Fields and the Supplementary Eye Fields via the Mediodorsal and VA of the Thalamus. The direct pathway beings with the cortex first stimulating the Striatum. The Striatum then inhibits the internal segment of the Globus Pallidus and the Substantia Nigra pars reticulata with the neurotransmitters GABA or Substance P (Sub P). leading to these structures being unable to inhibit the Thalamus rendering it free to fire and send excitatory input signals up to the Cortex, which facilitates movement.

The indirect pathway begins with the cortex stimulating the striatum (just like the direct pathway). Then Striatal neurons send inhibitory input to the external segment of the Globus Pallidus using the neurotransmitters GABA or Enkephalin (enk). The striatum inhibits the Globus pallidus from sending inhibitory signals to the Subthalamic Nucleus, the nucleus now being uninhibited sends only excitatory input within the Basal Ganglia pathways to the Globus Pallidus internal segment and the Substantia Nigra pars reticulate followed by these structures then inhibiting the VA and VL of the thalamus making it unable to send excitatory input to the Cortex and thus indirectly inhibiting the Motor Cortices, which inhibits movement.

The normal functioning Substantia Nigra pars compacta facilitates movement and inhibits unintended movement. It does this by exciting the direct pathway and inhibiting the indirect pathway through release of the neurotransmitter Dopamine. Striatal neurons have D1 and D2 receptors which are acted upon by dopamine to excite and inhibit them respectively. The Substantia Nigra pars compacta also sends excitatory input directly to the Cortex again using Dopamine.

**Cholinergic (ACh) Striatal Interneurons**

The cholinergic interneurons located within the Striatum synapse with the indirect and direct pathway with an effect antagonistic to that of dopamine. Release of ACh leads to the inhibition of the direct pathway and excitation of the indirect pathway. Parkinsonism is the result of the lesion of the substantia nigra which leads to its inability to excite the direct pathway nor inhibit the indirect pathway, this leads to the neurological manifestations associated with decreased movement. Dopamine when there is an increase in dopaminergic activity when an action has occurred, the circuit in the basal ganglia is modified to elicit the response even quicker if the same situation arises again. This is a form of reward signal in which dopamine plays a significant role [1].

**Addiction and reward centres in the brain**

Mesolimbic pathway, which involves the ventral tegmental area ending in the nucleus accumbens in the central striatum and extending into other areas such as amygdala, Bed Nucleus of Stria terminals, hypothalamus plays a key role in reward [11]. Various drugs are involved with this pathway by directly or indirectly interacting with different receptors of this pathway. Drugs such as Cocaine and amphetamine increase the synaptic action of Dopamine by blocking its presynaptic uptake and increasing its release from vesicles respectively [3]. Other drugs like phencyclidine (which blocks reuptake of dopamine and increase the cell firing of dopamine) [3,5], nicotine products (agonists at nicotinic cholinergic receptors), alcohol, heroin, morphine (activating dopamine via VTA GABAergic disinhibition) [3,4] and caffeine (an antagonist at striatal adenosine A2 receptors) [3,6] also acts on the mesolimbic pathway more so at the Nucleus accumbens and is responsible for the psychostimulant as well as rewarding effect.

Several authors have described possible specific cause triggering death of dopaminergic neurons in the substantia nigra, drug of abuse-induced neurotoxicity, is being considered as a potential mechanism to develop PD [7]. Effects of methamphetamine in Parkinson’s Disease on animal models have demonstrated loss of dopaminergic neurons and decrease in markers of dopamine such as Tyrosine Hydroxylase and Dopamine Transporter (DAT) [8].

Baumgarten and Zimmerman (1992) described several ways of cell death from ischemic damage, elevated intracellular calcium levels from glutamate excitation leading to cell death and direct neurotoxicity from the toxin which are formed by auto-oxidation of endogenous neurotransmitters (DA and 5-HT) [9].

**Discussion**

The aim of the article is to provide an overview of drug interactions with the limbic circuitry and conclude its involvement in the development of Parkinson’s or not. The given table below discusses different reports that conclude their observations on how different drugs maybe be involved in the development of Parkinson’s disease, the given table contains three columns of which the first states the

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report, the second states the drugs and/or their respective studies involved and the third concludes the report with results, observations or explanation of their mechanism of action in the development of Parkinson's. Here many drugs have been discussed, some with a higher propensity to Parkinson's disease as compared to others.

1) Common players reveal unexpected disease connections and novel therapeutic approaches. Gramage E1, Herradón G.

2) Methamphetamine/amphetamine abuse and risk of Parkinson's disease in Utah: A population-based assessment
Karen Curtin Annette E. Fleckenstein Reid J. Robison, Michael J. Crookston, Ken R. Smith, Glen R. Hanson

3) Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. Callaghan RC, Cunningham JK, Sykes J, Kish SJ.

1) Amphetamines and derivatives

2) A retrospective design was used to examine statewide medical records (1996 through 2011) linked to the Utah Population Database. Individuals 30 years or older on December 31, 2011 were assigned to a METH/AMPH cohort (ICD-9-CM 304.4, 305.7, 969.7, 8854.2; N = 4935), a cocaine cohort (ICD-9-CM 304.2, 305.6, 968.5, 8855.2; N = 1867) or a population cohort unexposed to drugs or alcohol for control selection. A competing-risks, proportional hazards model was used to determine whether the METH/AMPH or cocaine cohorts were at increased risk of developing PD (ICD-9-CM 332.0) or PD/parkinsonism/essential tremor (PD/PT; ICD-9-CM 332.0, 332.1, 333.0, 333.1) compared to individually sex- and age-matched controls (5:1 control to case ratio; N = 34,010).

2) n METH/AMPH users, we observed an increased risk of PD and PD/PT (HRPD = 2.8, 95%CI 1.6 - 4.8, P < 10 - 3; HRPD/PT = 3.1, 95%CI 1.9 - 4.9, P < 10 - 4) compared to population-based controls. Conversely, cocaine users exhibited no elevated risk of PD compared to controls.

3) A retrospective population-based cohort study was undertaken, using all linked statewide California inpatient hospital episodes and death records from January 1, 1990 through January 31, 2005. Patients at least 30 years of age were followed for up to

3) The meth/amphetamine cohort showed increased risk of PD compared to both that of the matched appendicitis group [hazard ratio (HR) = 1.76, 95% CI: 1.12 - 2.75, p = 0.017] and the matched cocaine group [HR = 2.44, 95% CI: 1.32 - 4.41, p = 0.004]. The cocaine group did not show elevated hazard of PD compared to the matched appendicitis group [HR=1.04, 95% CI: 0.56-1.93, p = 0.80].

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<th>16 years. Competing risks analysis was used to determine whether the meth/amphetamine cohort had elevated risk of developing PD (ICD-9 332.0; ICD-10 G20) in comparison to a matched population-proxy appendicitis group and a matched cocaine drug control group. Individuals admitted to hospital with meth/amphetamine-related conditions (n = 40,472; ICD-9 codes 304.4, 305.7, 969.7, EB54.2) were matched on age, race, sex, date of index admission, and patterns of hospital admission with patients with appendicitis conditions (n = 207,831; ICD-9 codes 540 - 542) and also individuals with cocaine-use disorders (n = 35,335; ICD-9 codes 304.2, 305.6, 968.5).</th>
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<tr>
<td>4) Substances of abuse and movement disorders: complex interactions and comorbidities Andres Deik, MD, Rachel Saunders-Pullman, MD, MPH, and Marta San Luciano, MD, MS</td>
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<td>4) The given report, describes the interaction of various drugs including beverages, which interact with the brain, which may lead to hypo or hyperkinetic disorders</td>
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<td>4) AMPHETAMINE-In mice, MDMA use causes ubiquitinated inclusions in the substantia nigra and striatum, and cases of parkinsonism have been reported in MDMA users [10-12]. However, the affect on primates and humans is up to debate [13-15]. COCAINE-lingering rest tremors has been detected in former abusers which is suggested to be proportional to the degree of use and inversely related to the length of time since the last use, [16] suggesting a toxic action on basal ganglia function though inhaled, it has been sometimes proved to ameliorate parkinsonian “off” periods in self-medicating patients without causing dyskinesias [17]. However, chronically it causes subtle parkinsonian features (such as tremor at rest) that could persist post withdrawal [16]. Methcathinone (Ephedrine) -its abuse results in a syndrome of levodopa-resistant, akinetic, rigid parkinsonism with myoclonus, speech dysfunction, bradyphrenia, gait and postural instability that very closely resembles a syndrome previously reported with manganese poisoning [17,18]. OPOIDS-Parkinsonism and bradykinesia are caused by opioid abuse [19]. Pallidal abnormalities in imaging and classical symmetric posterior fossa and supratentorial deep white matter changes [20], and cerebrospinal fluid studies have shown acute</td>
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5) Drug-induced parkinsonism following chronic methamphetamine use by a patient on haloperidol decanoate. Matthew BJ1, Gedzior JS2.

6) Neurological manifestation of chronic methamphetamine abuse. Daniel E. Rusyniak, MD

5) This report attempts to highlight that use of an antipsychotic and concurrent chronic use of methamphetamine can cause drug-induced parkinsonism.  

5) This case report describes just such a case of drug-induced parkinsonism which is a subacute syndrome that mimics Parkinson’s disease. Although less alarming than dystonia, it is more common, more difficult to treat and can be the cause of significant disability during maintenance treatment especially in the elderly. In most cases, symptoms are reversible in days or weeks, but occasionally, especially in the elderly, or if long-acting injectable antipsychotics are used-as in this case-symptoms may last for weeks or months.

Reduction of the dopaminemetabolite homovanillic acid (HVA) as well as the cofactor necessary for dopamine synthesis, tetrahydrobiopterin (BH4) [21], [22].  

Heroin-addicts that injected MPTP-containing “new heroin” developed acute, levodopa-responsive parkinsonism [20]. Inhalant exposure to solvents such as toluene, xylene and paint thinners may cause tremor, and, in chronic users, parkinsonism [23].  

Evolved-responsive parkinsonism has been found after 2 weeks of snorting heroin [24] but, in general, parkinsonian syndromes with encephalopathy after heroin abuse are rare.

6) One retrospective study, looking at hospital admissions over a ten-year period, found increased PD with history of methamphetamine abuse. Since it takes years for reductions in dopamine to reach the level of clinical symptoms, it is possible patients participating in these studies are not old enough to show symptoms; since most of studies include young adults. There have been two studies involving the same group of patients that support the idea of PD manifestations as there is a shift in age at which PD is abused. In a phone survey patient receiving care at one of three clinics, Patients who suffered from PD (OR = 8. CI 1.6 - 41) were more likely to

6) The prevalent theory is that abusing methamphetamine does not cause or play a role Parkinsonism. [25-27]. Several hypotheses suggest a discrepancy between the research and clinical data. [25-27]. The simplest is that they are different disorders. Parkinson’s disease acting on loss of dopaminergic neurons in the substantia nigra while methamphetamine abuse causes alterations in dopaminergic nerve terminals, but not acting on the cell bodies themselves. [26] In studies of methamphetamine abusers, they have greater dopamine reductions in the caudate compared to the putamen with Parkinson’s disease patients showing the opposite [26]. Another hypothesis is that after drug abstinence, the damaged dopaminergic nerve terminals begin to recover; decreased dopamine transporters of methamphetamine abusers were found to significantly recovery with prolonged (>12 months) abstinence [28]. Another hypothesis is that reduced dopamine levels represent a compensatory response to repeated elevations in monoamines. The strongest argument for this has been that the
<table>
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<th>7) Can cocaine abuse cause parkinsonism?</th>
<th>Dhopesh VP1, Yagnik PM, Weddington WW.</th>
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<td>have used amphetamines than their unaffected spouses and in the majority amphetamine abuse occurred long before symptoms even manifested [60]. Comparatively Parkinson’s patients without history of abuse to those patients with a history of amphetamine use were significantly younger at age of symptom onset, but not at age of diagnosis [35], however this is a small study and subject, by its design, to recall bias. Further investigations are required.</td>
<td>vesicular transporter-2 (VMAT2), which is known to be reduced in Parkinson’s disease and to be resistant to drug-compensatory regulation, is not significantly reduced in abstinent methamphetamine abusers but increases in abusers [29-31] it was hypothesized due to reductions in vesicular dopamine, depleted from recent release, leads to less dopamine being available to compete for binding to VMAT2 [31]. Another hypothesis involves nicotine and nicotine receptors. Acetylcholine nicotinic mechanisms that can affect the behavioral and neurochemical effects of psychomotor stimulant drugs and vice versa [32]. Most methamphetamine abusers are even cigarette smokers (87 - 92% vs 22%) [33]. Since cigarette smoking inversely correlated with development of PD114 methamphetamine abusers may be protected, or self-treated. [34] although it is still believed methamphetamine abuse still correlated with the development of PD [25,27,35].</td>
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<th>8) Drug-Induced Parkinsonism Hae-Won Shina and Sun Ju Chung</th>
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<td>8) study of effects (EPS) of the antipsychotic chlorpromazine found that about 40% of these patients showed parkinsons, 119 and several future studies found that DIP is the second most common etiology of parkinsonism [54-58].</td>
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<td>Citation: Kaushalendra Tripathi and Richa Tripathi. &quot;Parkinson's Disease and Drug Abuse&quot;. <em>EC Neurology</em> 7.3 (2017): 117-127.</td>
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9) Twenty-two patients with Parkinsonism were treated with levodopaamphetamine and 12 of these with dextroamphetamines.  

9) Levoamphetamines resulted in a significant improvement in disability from Parkinsonism, although the reduction in total disability, tremor, akinnesia, and rigidity scores was slight. Dextroamphetamine in lower dosage also reduced disability by some 17 percent. The most disabled patients, including those also on levodopa, showed the greatest response to amphetamines.  

10) Nonsteroidal antiinflammatory drug use and the risk for Parkinson's disease. Chen H1, Jacobs E, Schwarzschild MA, McCullough ML, Calle EE, Thun MJ, Ascherio A.  

10) Investigations whether nonsteroidal antiinflammatory drug use were associated with a lower risk for Parkinson's disease (PD) in a large cohort of US men and women.  

10) No association was found between the use of aspirin, other nonsteroidal antiinflammatory drugs, or acetaminophen and PD risk. The results suggest that ibuprofen use may delay or prevent the onset of PD.  


11) 71 Parkinson Study Group (PSG) investigators were using a standardized questionnaire about their use of antidepressants in PD. Based on estimates provided by 49 investigators (70%) (caring for approximately 23,410 PD patients) who responded, 26% of patients with PD are on pharmacotherapy for depression. These physicians use SSRIs as first line therapy 51% of the time, tricyclic antidepressants 41% of the time and other agents 8% of the time.  

11) Forty-three percent of investigators were concerned that SSRIs might worsen motor function, and 37% of them have had at least one patient in whom they believe this had occurred.
Results

Use of drugs such as heroin, Methcathinone, inhalants, amphetamines, cocaine as well as therapeutic drugs such as pro-kinetic and SSRIs may predispose persons to Parkinson’s disease though NSAIDs have no such association.

Conclusion

From the given observations in the table, cohort studies coupled with molecular studies have established a relationship between chronic amphetamine abuse and Parkinson’s disease, though cocaine use has not displayed a propensity to Parkinson’s disease, its chronic use may lead to subtle features of Parkinson’s disease, it may have therapeutic effects and ameliorate parkinsonian “off” periods, Methcathinone displays similar results to methamphetamine. Opioid abuse requires further studies to establish a relationship to its role in development of Parkinson’s disease, the contaminants in heroin abuse containing MPTP have developed acute, levodopa-responsive parkinsonism. Inhalant exposure to solvents such as toluene, xylene and paint thinners may cause tremor, and, in chronic users, parkinsonism. DIP (drug induced parkinsonism) has been observed in GI prokinetic drugs and SSRIs which also interact with the D1 and D2 receptor, especially as antagonists to D2, hence causing Parkinson’s disease. There is no association with the use of NSAIDS and Parkinson’s disease.

It is important to establish a direct correlation with replication of results on a cellular level basis or animal model to show the changes specifically expected from the patients that present with Parkinson’s disease at the clinics, further radiological studies such as fMRI, DTI scans and other various methods, maybe help with specific areas in addiction and clinically with Parkinson’s.

Bibliography


2) Shin HW and Chung SJ. "Drug-Induced Parkinsonism". (2012).


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22) Caligiuri MP and Buitenhuys C. "Do preclinical findings of methamphetamine-induced motor abnormalities translate to an observable clinical phenotype?". *Neuropsychopharmacology* 30.12 (2005): 2125-2134.

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