ANTIPSYCHOTIC DRUG-INDUCED DAMAGE IN THE BASAL GANGLIA AS A CAUSE OF PARKINSONISM: A REVIEW OF THE LITERATURE

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This project did not require approval from the Texas A&M University Research Compliance & Biosafety office.

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ABSTRACT

Antipsychotic Drug-Induced Damage in the Basal Ganglia as a cause of Parkinsonism: A Review of the Literature

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Parkinsonism refers to a set of conditions featuring motor symptoms such as slowness, tremor, and rigidity that are most commonly observed in older patients. Forms of Parkinsonism, including Parkinson's disease (PD) and drug-induced Parkinsonism (DIP), can be difficult to distinguish clinically and are associated with dysfunction in a subcortical brain region known as the basal ganglia, a group of structures which include the striatum. The basal ganglia receive dopaminergic projections from the substantia nigra pars compacta (SNc), and interfacing with the extrapyramidal system, these brain regions are critical in the regulation of involuntary and voluntary motor movements. Input from premotor areas and the cerebral cortex relay signals to the caudate and putamen forming the indirect and direct pathways. Both of which have competing, yet balanced, effects on movement. Reductions in either dopamine signaling or numbers of projecting neurons in these pathways leads to Parkinsonism. DIP can be initiated by dopamine receptor blocking agents, including first- (FGA) and second-generation (SGA) antipsychotic drugs, which block D_2 dopaminergic receptors. FGAs and SGAs primarily differ in

D_2 receptor affinity, with FGAs generally being higher. FGAs are more likely to cause DIP than SGAs, but despite the difference in receptor affinities, they are both capable of inducing motor deficits at varying concentrations. Unlike in PD, motor deficits in DIP may be alleviated upon withdrawal of the offending drug, but in some cases, patients continue to experience Parkinsonism symptoms for years. It is not known whether these more permanent forms of DIP may result from damage in the basal ganglia caused by FGAs and SGAs. Based on a review of the literature, evidence that prolonged exposure to, or high concentrations of these drugs, promotes neuronal dysfunction and induces permanent PD in patients is explored.

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NOMENCLATURE

PD	Parkinson's disease
DIP	Drug-induced parkinsonism
SNc	Substantia nigra pars compacta
FGA	First generation antipsychotics
SGA	Second generation antipsychotics
MSN	Medium spiny neurons
GPi	Globus pallidus internus
SNr	Substantia nigra pars reticulata
GPe	Globus pallidus externus
STN	Subthalamic nucleus
CSF	Cerebrospinal fluid
DAT	Dopamine transporter

INTRODUCTION

A motor disability composed of tremor, bradykinesia, rigidity, and postural instability was first described in 1817 by James Parkinson and was called the "Shaking Palsy" and is the disease we call Parkinson's today, but a range of symptoms are observed, and it can be accompanied by depression, emotional instability, and difficulties in cognition [1, 2]. The name Parkinson's Disease, or PD, was later suggested by Jean-Martin Charcot to better encompass these differences among affected individuals. PD can also be described by the broader term "parkinsonism," which refers to any disorder that causes motor symptoms of PD [1]. The neurodegeneration of dopaminergic neurons creates a permanence to the motor effects. PD is usually observed in elderly individuals and progresses with age, and rarely appears in those younger than 60 years old [3].

Beginning symptoms of PD are often difficult to detect. Later, symptoms progress and become more apparent, possibly a result of protein deposits called Lewy bodies that build up and disrupt the production of important neurotransmitters [4]. Other possible contributions to progression of the disorder include abnormalities in the motor loop of the basal ganglia [5]. Specifically, defects in the dopaminergic neurons that project from the substantia nigra and synapse onto striatal cells, where they normally release dopamine, are thought to play an important role [6]. These defects may include excessive cell death, mitochondrial dysfunction, abnormal signaling from astrocytes, and misfolding of the protein α-synuclein.

Drug-induced parkinsonism (DIP) is a form of the disorder caused by exposure to drugs, including primarily antipsychotic drugs, which block dopamine signaling in the basal ganglia. Since, both PD and DIP produce the same motor defects, DIP is often misdiagnosed as PD.

Patients with PD experience symptoms and neuron degeneration with increasing age. Meanwhile, patients with DIP may encounter symptoms at any age, but cases are most prevalent in old age [7]. The prevalence and degree of motor symptoms in DIP depend on which antipsychotics and doses were administered, and for how long. Furthermore, nuclear imaging techniques have shown distinct differences in the basal ganglia of affected patients, with PD patients having asymmetrical defects across the two hemispheres, whereas in DIP they are symmetrical [8].

1. NEUROANATOMICAL BASIS FOR THERAPEUTIC AND SIDE EFFECTS ASSOCIATED WITH ANTIPSYCHOTIC DRUG TREATMENT

Antipsychotic drug treatment is most commonly given for illnesses with psychotic features, including schizophrenia. These drugs are known to have many adverse side effects due to their effect on several different neurotransmitter systems, including their profound antagonism of dopamine receptors. Dopamine receptors, found throughout the brain, are guanine nucleotide binding protein (G-protein) coupled receptors that are bound to the membrane. They are located both presynaptically and postsynaptically, and there are five different dopamine receptors: D_1, D_2, D_3, D_4, and D_5, the functions of which are shown in Table 1 [9]. Dopamine D_1 and D_5 receptor subtypes are collectively called D1-type, while D_2, D_3, and D_4 subtypes are called D2-type, and they initiate, or inhibit, the cyclic AMP (cAMP) second messenger pathway, respectively, to produce a cellular response [10]. Both D1- and D2-types are located postsynaptically on striatal GABAergic neurons, known as medium spiny neurons (MSNs), while D2-type are additionally found on cholinergic interneurons in the basal ganglia. D1-expressing MSNs make up the direct pathway, the stimulation of which activates inhibitory striatal efferents directly onto the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr). D2-expressing MSNs make up the indirect pathway of the brain, another set of inhibitory striatal neurons that indirectly project to the SNr by way of the globus pallidus externus (GPe) and subthalamic nucleus (STN). Both pathways receive initiating signals from the cortex and send information to the thalamus, where they have opposing net effects [11]. Dopamine production and release levels are additionally influenced by D_2 receptors located presynaptically on dopaminergic neuron terminals, and dopamine is cleared from the synapse by

the dopamine transporter, or DAT, which is also located presynaptically. Degeneration of the neurons that release dopamine directly affects dopaminergic receptors, making them unable to project signals that are responsible for coordinated movement output [12].

Table 1: The Five Dopamine Receptor Sub-Types and Functions [9].

Dopamine Receptor Types	Dopamine Receptor Function
D_1	Locomotion, attention, sleep, regulation of renal function, impulse control, learning, and memory
D_2	Locomotion, attention, sleep, reproductive behavior, learning, and memory
D_3	Locomotion, attention, sleep, cognition, impulse control, and regulation of food intake
D_4	Cognition, attention, sleep, impulse control, and reproductive behavior
D_5	Cognition, attention, decision making, renin secretion, and motor learning

While it is somewhat controversial, it is thought that antipsychotics have their primary therapeutic effect, correcting the positive symptoms (e.g., hallucinations) in schizophrenia, for example, by blocking D_2 receptors in the limbic system. However, these drugs have affinity for all D_2 receptors throughout the brain [14], and their blockade in the basal ganglia and resulting negative impact on the extrapyramidal system cause problems relating to locomotion. The extrapyramidal system is a network of brain regions that includes the basal ganglia, cerebellum, premotor, and supplementary motor areas, which are responsible for voluntary and involuntary movement.

Antipsychotic drugs are split into two different classes based on when they were developed. First-generation antipsychotics (FGAs), developed earlier, have higher affinities for the dopamine D_2 receptor and are two times more likely to cause DIP than second-generation antipsychotics (SGAs), as shown in Table 2. Chlorpromazine, an example of an FGA, induces parkinsonism in 40% of users and aripiprazole, an SGA, induces parkinsonism in over 2% of users [15, 13]. In addition, FGAs are more likely to cause persisting DIP, lasting months to years after withdrawal of the drug. DIP percentages today are much better than they were at the time of FGA production because of the development of SGAs, decreasing the likelihood of parkinsonism [16]. SGAs quetiapine and clozapine have been shown least likely among the antipsychotics to produce DIP in patients [17]. However, it is important to note that both SGAs and FGAs are known to treat positive schizophrenic symptoms well, and FGAs are still in use [18].

Table 2: FGA and SGA Parkinsonism Adverse Effect Frequency [13].

Antipsychotic Class	Compound	Adverse Effect Frequency
FGA	Chlorpromazine	Moderately frequent
FGA	Fluphenazine	Frequent
FGA	Haloperidol	Frequent
FGA	Trifluoperazine	Frequent
SGA	Amisulpride	Moderately frequent
SGA	Aripiprazole	Infrequent
SGA	Clozapine	Infrequent
SGA	Olanzapine	Infrequent
SGA	Quetiapine	Infrequent
SGA	Risperidone	Moderately frequent

2. POSSIBLE MECHANISMS UNDERLYING DIP

DIP is estimated to appear days to weeks after treatment with antipsychotics has begun, but in some cases, DIP appears years after the drug is discontinued. The average DIP patient taking antipsychotic drugs should be able to withdraw from the FGA or SGA and recover from all extrapyramidal motor symptoms within days to years. However, a number of factors can interfere with this process. Some patients with severe symptoms from psychotic disorders may be unable to discontinue the offending drug. If possible, patients taking FGAs in this situation may be changed to SGAs to attempt the reduction of DIP and continue management of psychotic symptoms. Long-term exposure or high concentrations of SGAs are more likely to promote DIP [7], thus patients that require the assistance of FGAs or SGAs in higher concentrations should be routinely monitored.

The basal ganglia contain high levels of catecholamines and iron, which in radical form can induce oxidative stress. Previously, it was found that prolonged administration of antipsychotics in patients experiencing extrapyramidal side effects is associated with an increase in protein carbonyl oxidation products, an increase in markers of oxidative stress in the cerebrospinal fluid (CSF), and their symptoms are negatively correlated with superoxide dismutase levels. Reductions in superoxide dismutase, an enzyme that mediates partitioning (dismutation) of the superoxide radical into oxygen and hydrogen peroxide, allow more oxidative stress and neuronal damage to occur and may relate, specifically, to the degeneration of striatal GABAergic neurons. Decreased superoxide dismutase is reported in schizophrenia patients that are most prone to DIP [19].

The number of glutamatergic corticostriatal synapses increases as a result of antipsychotic treatment, specifically haloperidol. D_2 receptor blockade on corticostriatal glutamate neurons increases the release of the neurotransmitter glutamate by 50% [20]. Clozapine and sulpiride, SGAs, were found unable to increase striatal glutamate indicating that they are not likely to induce extrapyramidal side effects [21]. The increased number of glutamatergic corticostriatal synapses, which decrease upon withdrawal, may be related to the developed tolerance that can be observed for extrapyramidal symptoms [20]. Haloperidol was found to increase glutamate release in the corpus striatum, and the authors concluded that it and perhaps other FGAs are more likely than SGAs to impact this region strongly [22].

Another study found evidence of haloperidol toxicity by analyzing elevated plasma levels of membrane lipid peroxidation, which is associated with oxidative stress that causes neurodegeneration. FGA, and specifically haloperidol, -treated patients showed an increase in lipid peroxidation unlike those treated with the SGA olanzapine. Patients taking haloperidol expressed significantly reduced levels of antioxidants, including ascorbate and alpha tocopherol. As both are required in the process of interrupting free radical propagation, these changes may upset the balance of redox reactions [23, 24].

Previous research has attempted to use this information to investigate prevention of the development of DIP. Vitamin E is a known antioxidant, able to break down oxidative substances in the nigrostriatal pathway [24, 25]. One study found that combining vitamin E with antipsychotic drugs, haloperidol, perphenazine, and chlorpromazine, in patients with schizophrenia resulted in a trend towards increased prevention of DIP without affecting the antipsychotic's ability to treat symptoms. However, there was no evidence of vitamin E lessening the severity of akathisia, another antipsychotic-induced movement disorder. Despite

limitations on the number of subjects in the study, vitamin E should be further investigated for its potential in clinical practice [26].

3. DOPAMINE TRANSPORTER IMAGING COMPARATIVE EFFECTS OF ANTIPSYCHOTIC DRUG USE

As mentioned, the DAT, or dopamine transporter, is located on the presynaptic side of dopaminergic synapses and functions to reuptake extracellular dopamine back into the presynaptic terminal. Movement of dopamine back into the presynaptic neuron ensures that dopamine signaling remains brief and meaningful in the conveyance of information and maintains a normal level of synaptic influence over motor output. The DAT can be visualized using non-invasive imaging technologies, such as single photon emission computed tomography (SPECT), as well as positron emission tomography (PET), to determine its location and concentration in the brain [27]. Both techniques involve the usage of radioligands that are fused to drugs having high affinity for and that reversibly bind to the DAT, making them safe for use clinically. SPECT scans utilize *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-^{123}I-iodophenyl)nortropane (^{123}I-FP-CIT) and ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane (^{123}I-β-CIT). ^{123}I-FP-CIT has more affinity to DAT and faster kinetic properties than ^{123}I-β-CIT [28]. PET scans utilize [^{18}F]-(E)-*N*-(3-iodoprop-2-enyl)-2β-carbofluoroethoxy-3β-(4′-methyl-phenyl)nortropane (^{18}F-FE-PE2I) and ^{11}C-*N*-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methylphenyl)nortropane (^{11}C-PE2I). ^{18}F-FE-PE2I has a greater affinity for DAT than ^{11}C-PE2I [29]. All PET and SPECT radioligands are primarily used for research purposes except for ^{123}I-FP-CIT, which is used for medical practices [30].

Guidelines for interpreting SPECT suggest that DAT-binding can indicate presynaptic dopamine terminal presence and may be used to distinguish in subclinical PD from DIP [31]. Using this method, another study addressed the confusing fact that incompletely recovered DIP

patients still experience the physical symptoms of DIP while expressing what appears to be normal DAT density. The authors compared DIP patients that were partially recovered and completely recovered using ^{18}F-FP-CIT PET scan and used a semi-quantitative analysis that allowed relative density comparisons. Their findings showed that partially recovered patients indeed have slightly decreased DAT binding in the ventral striatum and putamen compared to fully recovered, but this difference may not be appreciated or recognized in basic imaging findings. The authors conclude that continued parkinsonism in partially recovered patients is likely due to this subtle reduction in DAT activity [32].

CONCLUSION

In conclusion, the findings reported in the literature support that antipsychotics are capable of producing permanent forms of PD. Evidence of impaired antioxidant defense in patients treated with antipsychotics suggests neurotoxicity is caused by FGAs, especially haloperidol. Given that DIP is more likely to appear in the elderly, damage induced by antipsychotics or other drugs may interact with naturally occurring age-related reductions in dopaminergic neuron function. These findings suggest that patients should receive DAT-binding imaging using SPECT, or similar techniques, upon initial appearance of any motor dysfunction characteristic of DIP and PD, which may help to determine proper clinical diagnosis. In addition, screenings should be done routinely for patients taking antipsychotics to document signs of parkinsonism and determine change over time within-patient. Lastly, administration of vitamin E should be investigated further as an option that can reduce the severity or likelihood of DIP in patients taking antipsychotic drugs.

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