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Dopamine based Pharmaco-therapeutics of Schizophrenia and Parkinson's Disease: Two Ends of One Spectrum

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Abstract

Schizophrenia and Parkinsons's disease are two neuro-pathological end points of dopaminergic spectrum in the mid brain. While the symptoms of Parkinson's disease results from the death of dopaminergic cells in substantia nigra, the psychotic symptoms of schizophrenia are related to dopaminergic hyperactivity in the striatum. Pharmacological intervention therefore involves normalizing the dopamine concentrations, wherein dopaminergic drugs are used to treat patients with Parkinson's disease, dopamine antagonists are used to treat patients with schizophrenia. These pharmacological interventions in either of the two disease states, results in over shooting the optimum dopamine levels, therapy resulting in drug induced extra-pyramidal symptoms in schizophrenia and hallucinations in Parkinson's disease. This review summarizes the side effects observed using dopamine modulating pharmaceuticals, and brings to light the clinical scenario of drug induced disease state at both ends of dopamine spectrum, that poses a challenge to patients and clinicians.

Keywords: Schizophrenia; Parkinson's disease; Dopamine; Adverse side effects; Treatment monitoring

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Introduction

Parkinson's disease is a degenerative disorder of the central nervous system and schizophrenia is a mental disorder characterized by a breakdown of thought processes with deficit of emotional responses. While the motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, the psychotic symptoms of schizophrenia are related to dopamine hyperactivity in the striatum. These two diseases are therefore end points of the dominergic activity spectrum in the mid brain.

The prevalence of Parkinson's disease is about 0.3% of the whole population in industrialized countries. Parkinson's disease is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80 [1]. The incidence of Parkinson's disease is between 8-18 per 100,000 person-years [2]. Schizophrenia affects around 0.3-0.7% of people at some point in their life or 24 million people worldwide as of 2011 [3,4]. It occurs 1.4 times more frequently in males than females and typically appears earlier in men [5]. The peak ages of onset are 20-28 years for males and 26-32 years for females [6]. Onset in childhood is much rarer and is usually seen in middle or old age [7]. Its prevalence varies across the world within countries, and at the local and neighbourhood level [8,9]. It causes approximately 1% of worldwide disability for adjusted life years and resulted in 20,000 deaths in 2010 [10]. In India, Parkinson's disease has been known since ancient days. The present day management of Parkinson's disease in India is similar to that in other countries. Unfortunately lack of awareness, limitations of human resources and cost factor deny the benefits of therapy to many patients [11]. The alarming rise in the prevalence of Parkinson's disease in India has been attributed to the demographic pattern, changing environment as well as lifestyle and socio-economic status [12,13]. Epidemiological studies show considerably higher prevalence of Parkinson's disease amongst white compared to non-white populations. In one particular study using United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria diagnosed Parkinson's disease in 84 of 493 residents. Of these 84, 80 were Indians and 4 were Anglo-Indians. Occurrence of Parkinson's disease is nearly five times higher amongst Indians compared to the Anglo-Indians [14].

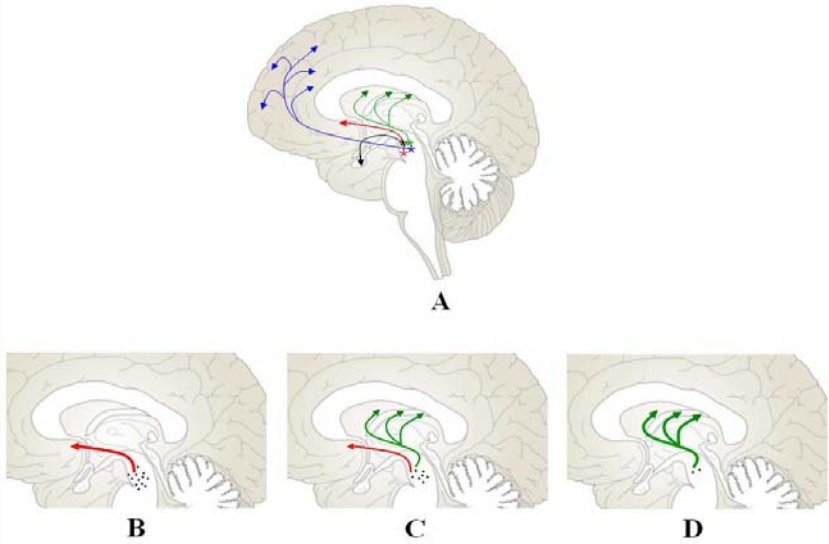

Figure 1: Dopaminergic pathways in the Brain: (A) meso-corical pathway transmits dopamine from the ventral tegmental area to the frontal lobe of the pre-frontal cortex (blue), meso-limbic pathway transmits dopamine from ventral tegmental area to nucleus accumbens (red), nigro strial transmits dopamine from substantia nigra to striatum (green), and tubero-infundibular pathways transmits dopamine from the infundibular nucleus in the hypothalamus to the pituitary gland (black); (B) hyper-activation of D2 receptor dopaminergic function of meso-limbic pathway resulting in schizophrenia; (C) normal physiological pathways of mesolimbic and nigro-strial pathways; (D) reduced D2 receptor dopaminergic function of nigro-strial pathway resulting in Parkinson's disease. Black dots represent dopamine.

Dopaminergic neuro-transmission as molecular pathogenesis in Parkinson's disease and schizophrenia

Dopamine is a simple organic chemical in the catecholamine and phenethylamine families. It is an amine that is formed by removing a carboxyl group from a molecule of L-DOPA. In the brain, dopamine functions as a neurotransmitter which is released by certain specific nerve cells to send signals to other nerve cells. Dopamine exerts its effects by binding to and activating receptors located on the surface of cells. In mammals, five subtypes of G protein-coupled dopamine receptors D1 through D5 have been identified, of which D2 receptor is the predominant one in connecting the collaterals in basal ganglia thereby having a potential implication in health and disease [15]. The end effect of dopamine on a target neuron depends on the types of receptors are present on the membrane of that neuron. There are four important pathways that have dopamine as their main neuro-transmitter. They are: Nigrostriatal pathway, Mesolimbic pathway, Mesocortical pathway and Tuberoinfundibular pathway (Figure 1A). The D2 receptors are higher in number in the mesolimbic pathways and nigrostrial pathways, and are the molecular basis for patho-physiological understanding of Parkinson's disease and schizophrenia. As the review pertains to side-effects of drugs that lead to dopamine alterations in these two pathways, the subsequent discussions will therefore pertain to these two mesolimbic pathways and nigrostrial pathways. The involvement of tubero-infundibular pathway mediated hyper-prolactinemia in patients taking dopaminergic antagonists is known, but is not discussed in this review [16].

The mesolimbic pathway transmits dopamine from the ventral tegmental area to the nucleus accumbens, and includes the amygdala and the hippocampus. Meso-limbic pathway is a dopaminergic pathway that connects ventral tegmental area, located in the midbrain, to the nucleus accumbens which is located in the ventral striatum [17]. The release of dopamine into the nucleus accumbens regulates incentive based emotions like motivation and desire for rewarding stimuli and facilitates reward-related motor function learning [18]. The striatum of schizophrenia patients displays augmentation of pre-synaptic dopamine function, indicating an increase in dopamine synthesis capacity and/or an increase in pre-synaptic dopamine stores [19-21] (Figure 1B). Recent evidence indicates that these alterations in dopamine function are particularly apparent in the associative subdivision of the striatum which predominantly receives projections from the substantia nigra [22-26]. An increase in pre-synaptic dopamine synthesis in neuroleptic naïve schizophrenia subjects is also indicated by an increase in homovanillic acid and elevations in striatal dopaminergic receptors [20,27-32]. Also, schizophrenia is associated with elevations in striatal dopamine synthesis capacity, as measured using the PET radiotracers [33]. This excessive augmentation of meso-limbic system results in hallucinations, which is one of the main positive symptoms seen in schizophrenia [34]. It may be noted that 5-HT receptors form the bulk of the receptors in the mesocortical pathways that mediate the negative symptoms of schizophrenia.

The nigrostriatal pathway or nigrostriatal system transmits dopamine from the substantia nigra to the neostriatum that includes the caudate nucleus and the putamen, to generate smooth and purposeful muscle activity (Figure 1C). However, in Parkinson's disease there is loss of midbrain dopaminergic neurons of the substantia nigra, pars compacta, and of their terminals in the striatum [35,36] (Figure 1D). Dopamine-producing cells in the substantia nigra may be lost to the extent of 80% thereby causing the nerve cells of the striatum to fire out of control, thereby resulting in symptoms of dystonia, akathisia, rigidity, bradykinesia and tardive dyskinesia.

Drug based therapeutics of Parkinson's disease and Schizophrenia

The treatment of Parkinson's disease includes pharmacological interventions that aim to increase the availability of dopamine in the neurons of the brain. L-DOPA, a precursor for dopamine that is taken orally is absorbed from the gut and reaches the brain through the blood stream. It is converted to dopamine that is transported to the synapse where it acts as a neuro-transmitter. While the available L-DOPA constitutes only a fraction of the consumed drug, a majority

Table 1: Schizophrenia therapy and its side effects. FGA: First Generation Antipsychotics; SGA: Second Generation Antipsychotics; + indicates atypical or SGA.

No.	Disease	Therapy	Side effects	Reference
1	schizophrenia	FGA & SGA	extra-pyramidal symptoms	[39]
2	schizophrenia	FGA & SGA	extra-pyramidal symtoms	[40]
3	schizophrenia	clozapine†	Parkinsonism	[41]
4	schizophrenia	SGA (except clozapine)	extra-pyramidal symptoms	[42]
5	Psychosis	olanzapine† & risperidone†	Parkinsonism, dyskinesia, akathisis, dystonia, catatonia	[43]
6	schizophrenia	FGA & SGA	tardive dyskinesia	[44]
7	schizophrenia	risperidone†	motor side effects	[45]
8	schizophrenia	perphenazine, SGA	extra-pyramidal symptoms	[46]
9	schizophrenia	loxapine, risperidone†	extra-pyramidal symptoms	[47]
10	schizophrenia	haloperidol	Parkinsonism, akathisia	[48]
11	schizophrenia	perphenazine & SGA (except clozapine)	extra-pyramidal symptoms	[49]
12	schizophrenia	SGA (except clozapine)	extra-pyramidal symptoms	[50]
13	schizophrenia	SGA (except clozapine)	sensori-motor dysfunction	[51]
14	schizophrenia	olanzapine†, haloperidol	Extra-pyramidal symptoms	[52]
15	schizophrenia	ziprasidone (SGA)	acute dystonia	[53]
16	schizophrenia	ariprazole, risperidone†	extra-pyramidal symptoms	[54]
17	schizophrenia	haloperidol, clozapine†	Parkinsonism, akathesia	[55]
18	schizophrenia	haloperidol, olanzapine†	tardive dyskinesia	[56]
19	schizophrenia	risperidone†, haloperidol	Parkinsonism, dystonia, dyskinesia	[57]
20	schizophrenia	haloperidol	extra-pyramidal symptoms	[58]

of the drug is broken down by the enzyme L-DOPA de-carboxylase in the blood and the enzyme COMT in the brain. These enzymes are therefore the drug targets for inhibition by molecules such as carbidopa and tolcapone. Agonists of dopamine and mono-amino oxidase inhibitors help to either mimic dopamine or increase the availability of the same at the dopamineric receptors, respectively. The therapeutic intervention in cases of schizophrenia includes medications that include dopaminergic blockade in the limbic system and basal ganglia. All currently available medical treatments for schizophrenia reduce the activity of dopamine as a signal between neurons in the brain. Antipsychotic effects of traditional 'neuroleptic' drugs are highly correlated with their ability to block dopamine receptors and reduce the effects of dopamine.

Side effects of pharmacological medications in Parkinson and Schizophrenia

Pharmacological medications and response in Parkinson's disease and schizophrenia revolve around the levels of dopamine in the brain [37]. All medications used to treat Parkinson's disease could cause psychotic Schizophrenia type symptoms in those taking the medications for symptoms. Parkinson's medications act by adding dopamine to the body. However during the course of the therapy, the dopamine levels tend to increase above the normal levels leading to symptoms of Schizophrenia. Likewise, the problem in using neuroleptic drugs in the treatment of schizophrenia is that the neuroleptic drugs lower the amounts of dopamine and may adversely produce symptoms of side-effects of tardive dyskinesia, tremors, pin-rolling of the fingers, shuffling gait and a mask-like facial expressions which are all features of Parkinson's disease [38]. Table 1 depicts clinical case studies and meta-analyses investigating the emergence of dug induced Parkinsonism in patients who underwent anti-psychotic drug therapies for schizophrenia [39-58]. Currently, two classes of anti- psychotics are used in the clinical setting. They are first generation anti-psychotics that are dopamine antagonists and second generation anti-psychotics that exert their therapeutic effects by moderate D_2 antagonism along with serotonin blockade. Extra-pyramidal symptoms of first generation drugs have been established and the induced side effects of this class of therapeutics include akathisia, tardive dyskinesia and motor symptoms reminiscent of Parkinsonism [48]. Second generation atypical anti-psychotics were introduced for the first time in the year 1990 and endorsed as deficient of extra pyramidal motor symptoms. However recent literature from case studies point to the contrary. Extra pyramidal symptoms have been reported for this class of anti-psychotics [39, 43, 49]. The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review aimed at identifying evidence-based optimal use in prescription of anti-psychotic drugs and reported that second generation anti-psychotics were capable of exerting side effects related to extra pyramidal symptoms and drug induced Parkinsonism [42]. Interestingly, as per the recent studies atypical anti-psycotic drugs including clozapine too have been associated with extra pyramidal side effects. [59].

Table 2 illustrates the literature citing several clinical studies and meta-analyses that portray the psychotic side effects arising out as a result of anti-Parkinson's therapy [60-80]. As can be inferred, almost every class of anti-Parkinson drug that includes dopamine replacement therapy, dopaminergic agonists and mono amino oxidase B inhibitors exhibit adverse effects. Most of these adverse effects pertain to psychotic manifestations of auditory/visual/tactile hallucinations, compulsive tendencies and delusions which in-turn are the major hallmarks of schizophrenia. Most recently, in a case study of early onset Parkinson's disease, the patient exhibited delusions, hallucinations and compulsive gambling following a therapeutic regimen of dopamine replacement and dopaminergic agonists [61]. Moreover, it has been observed that adjunctive therapies like MAO-B

Table 2: Parkinson's disease therapy and its side effects.

No.	Disease	Therapy	Side effects	Reference
1	Early onset Parkinson's disease	dopaminergic replacement	hallucinations	[60]
2	Early onset Parkinson's disease	dopaminergic replacement	delusions, hallucinations, compulsive gambling	[61]
3	Parkinson's disease	dopaminergic replacement	visual/auditory/somato-sensory hallucinations, delusions	[62]
4	Parkinson's disease	dopaminergic replacement	psychosis	[63]
5	Parkinson's disease	dopaminergic replacement	visual/auditory hallucination, paranoid ideation, misidentification	[64]
6	Parkinson's disease	dopaminergic replacement	visual hallucinations, nightmares	[65]
7	Parkinson's disease	dopaminergic replacement	insomnia, persecutory delusions, visual & auditory hallucinations	[66]
8	Idiopathic Parkinson's Disease	dopaminergic replacement	depression, thought disorder, hallucinations, sleep disturbance	[67]
9	Parkinson's disease	dopaminergic replacement	vivid dreams, hallucinations	[68]
10	Parkinson's disease	dopaminergic replacement	hallucinations, delusions, florid psychosis	[69]
11	Parkinson's disease	pergolide	psychosis	[70]
12	Parkinson's disease	dopaminergic replacement	visual & auditory hallucinations	[71]
13	Parkinson's disease	dopaminergic replacement	hallucinations, delusions, destructive behaviour	[72]
14	Parkinson's disease	dopaminergic replacement	illusions, frank hallucinations, delusion, paranoia	[73]
15	Parkinson's disease	dopaminergic replacement	psychosis	[74]
16	Parkinson's disease	dopaminergic replacement	vivid hallucinations, Suspicion, paranoia	[75]
17	Parkinson's disease	dopaminergic replacement	delusions, hallucinations, paranoia	[76]
18	Idiopathic Parkinson's disease	dopaminergic replacement	psychosis	[77]
19	Parkinson's disease	dopaminergic replacement	psychosis	[78]
20	Parkinson's disease	dopaminergic replacement	hallucinatory delusions	[79]
21	Parkinson's disease	dopaminergic replacement	hallucinations	[80]

inhibitors that aim to increase the overall availability of dopamine at the receptors and anti-cholinergics which act at cholinergic receptors are also not devoid of psychotic side effects as evidenced by the emergence of frank and persecutory delusions, paranoia and hallucinations [73,74,76].

Importance of defining the state of optimum therapy

Pharmacological intervention is the mainstay of treatment for Parkinson's disease and Schizophrenia. It is quite clear from the above review of literature that there is a high chance of overshooting the point of normal dopaminergic state, add patient may succumb to the side effect which is the disease at the other end of the dopaminergic spectrum. There are currently no laboratories tests that aid in monitoring therapy or help predict adverse side effects of the drugs used. The clinicians are forced to rely completely on the patient response to understand the efficacy of the drug. This causes a lot of inconvenience to the patients, patient attendants and the clinicians. This drawback also has an indirect impact on the financial expenditures on the patients, hospitals and the state. Clinical proteomics in central nervous system disease is an ideal platform for biomarkers discovery [81,82]. This will help immensely to assess effective treatment response and optimise pharmacological intervention in Parkinson's disease and Schizophrenia.

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