DOI: http://dx.doi.org/10.47690/JNN.2019.1101

Open Access Journal | Volume: 1.1

JOURNAL OF NEUROPSYCHIATRY AND NEURODISORDERS

Tardive Dyskinesia and Akathasia: A Dopamine System Theory Clinical Review

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Article Information

Article Type: Review

Journal Type: Open Access

Volume: 1 **Issue:** 1

Manuscript ID: JNN-1-101

Publisher: Science World Publishing

Received Date: 04 January 2019

Accepted Date: 25 January 2019

Published Date: 28 January 2019

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Citation: Dr. Tammi McGill-Carter (2019), Tardive Dyskinesia and Akathasia: A Dopamine System Theory Clinical Review. J Neuropsychiatr Neurodis, 1(1);1-2

ABSTRACT

Long term use of first-generation Anti-psychotics (FGAs) have been theorized in the formation of motion disorders Tardive Dyskinesia and Akathasia and due to the breakdown in the Extra Pyramidal System (EPS) located in the Basal Ganglia (Lehne, 2013). The Second-generation Anti-psychotics (SGAs) were sourced to be the "treatment" of TD by blocking dopamine receptors with dopamine agonists of the D2-D5 receptors while also being seen as the genesis of AK. However, the blocking of the receptors in both motion disorders is a theory known as the dopamine blockage theory, despite the intermingle of other neurotransmitters such as Serotonin and Norepinephrine (Lieberman, Stroup, McEnvoy, Swartz, Rosenheck, & Perkins, 2005).

KEYWORDS

Anti-psychotics, Dopamine, Dyskinesia and Akathasia, Clozapine and Mirtazapine

INTRODUCTION

The EP system includes theorized Dopamine and Serotonin connections within the Basal Ganglia, the striatopallidongral system, and other structures of the central nervous system that contribute to the regulation of movement, including brainstem nuclei and the cerebellum (Jibson, Marder, & Hermann, 2018). One example of a classical disorder of the pyramidal system is a stroke, resulting in paralysis of an extremity. Cortiospinal lesions above the pyramidal decussation typically result in paralysis of volitional movements of the contralateral half of the body (Patterson, McCahill, & Edwards, 2010).

The pathophysiology of EPS disorders has been disputed because some EPS disorders may not involve lesions of the Basal ganglia. In addition, motions associated with said disorders may not be involuntary (Jibson, et al., 2018; Patterson, et al., 2010). Because of the problems inherited in the concept of the EPS, caution must be exercised in the classification of the EPS due the countless symptoms that mimic other motion disorders as certain neurotransmitters can create the actions of another.

Pathophysiology of Tardive Dyskinesia

The central dopamine blockage theory states that the long-term use of dopamine antagonists (FGAs) has been hypothesized to play a role in the pathogenesis of TD (Guzman & Farinde, 2016; Lehne, 2013). This disorder is described as Bucco-Masticatory and the rigid movements of the lips, tongue, face, trunk, and upper extremities. The theory has also hypothesized that the result of TD is due in part of the compensatory super sensitivity of dopamine receptors following a chronic blockade of the D antagonists (Lieberman, et al., 2005).

Although the D2 receptor has traditionally been implicated in the pathogenesis of TD, mounting evidence indicates that, in some individuals, the dopamine D3, D4, and D5 receptors are involved (James & Bendadis, 2010). TD has been associated with polymorphism of both the dopamine receptor D2 gene, Taql A and Taql B and the associated haplotypes, and of the dopamine receptor D3 gene (Lieberman, et al., 2005).

Pathophysiology of Akathasia

While the dopamine hypothesis is the most documented theory of Akathisia to date much like TD, it is unlikely that a single neurotransmitter hypothesis can explain all the complexities of this disorder. In fact, the interaction of several NT's such as Norepinephrine are involved with the developmental of TD's sidekick, Akathasia. This specific disorder affects the lower extremities and is known as restless leg syndrome (Kumar

& Perminder, 2009; Kolb & Whishaw, 2009).

Another well hypothesized theory of the genesis of Akathisia are the long-term use of Second-Generation Antipsychotics (SGAs) that function on the serotonergic system. Such drugs include Haldol, SSRI's such as Fluoxetine and Paroxetine, and Abilify also known as mood stabilizers (Patterson, 2010; Pies, 2005; Preston & Johnson, 2012).

More serotonin effects include opioid withdrawal, Cocaine withdrawal (Mostly heavy and long-term users), Cannabis and Alcohol withdrawal (Pies, 2005). Despite the serotonin system effects by SGA's, the dopamine hypothesis that applies to TD also applies to Akathisia as well, Dopamine receptor blockade, only the blockage with Akathisia is caused by SGA's is on the D2 receptor occupancy.

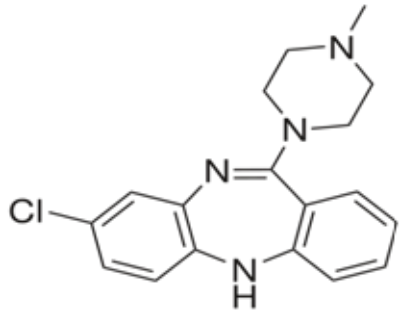
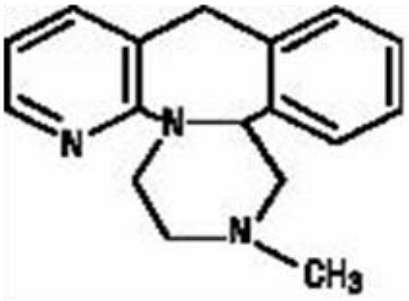
Selected Treatments

The only drug treatment listed for the treatment for TD to date is Clozapine (Clozaril) (Young, Bowers & Mazure, 1998). Clozapine was first developed by Sandoz Pharmaceuticals in 1961, but was discovered in Europe in 1975 (Young et al., 1998; Stenberg, Terevinkov, Joffe, Tiihonen, Tchoukhine, Burken, & Joffe, 2010). Clozapine was normally prescribed to treat Schizophrenia, Bipolar disorder, but after several experimental trials, the scientific community discovered that Clozapine is also helpful with TD and Akathisia (Stenberg, et al., 2010). Clozapine works on the same dopamine receptors (D1-D5) with an affinity for the D4 receptor for TD and Akathisia patients.

While Clozapine has been discovered to help TD and Akathisia patients, Mirtazapine, next to Clozapine, has been prescribed to treat the symptoms of Akathisia (Alam, Voronovich, & Carley, 2013). The route for both drugs is oral administration. The bioavailability for Mirtazapine is 50% and is metabolized in the liver by the CYP2D6 and CYP3A4 enzymes (Alam et al., 2013). Clozapine is never truly complete due to its bioavailability being 60-70% at first pass metabolism of the liver. Clozapine is extensively metabolized in the liver, via the cytochrome P450 system, to polar metabolites suitable for elimination through either the feces or urination (Alam, et al., 2013; Stenberg, et al., 2010; Kolb & Whishaw, 2009).

Mechanisms of Action of Clozapine and Mirtazapine

Clozapine is more active in the limbic system rather than at the striatal dopamine receptors and may explain the relative freedom of Clozapine from extrapyramidal side effects with strong anticholinergic activity (Kolb & Whishaw, 2009). Clozapine is also a partial agonist at the 5-HT1a receptor, putatively improving depression, anxiety, and negative cognitive symptoms (Young et al. 1998). Clozapine has the profile of binding to Serotonergic and Dopaminergic receptors (Kolb & Whishaw, 2009). Tetracyclic antidepressants, that such as Mirtazapine, acts by increasing the central noradrenergic serontonic neurotransmission (Stenberg et al., 2010). Mirtazapine appears to act primarily on the postsynaptic 5-HT2 and 5-HT3 and central a1 (adrenergic) receptors. With long term use of Clozapine, the dissolution or death of white blood cells, known as Agranulocytosis (Kolb & Whishaw, 2009; Young et al., 1998).

Clozaril	Mirtazapine
	

Agranulocytosis

The development of agranulocytosis is a medical emergency. Agranulocytosis is defined as a granulocyte count of < 500/mm^3 and leukopenia is defined as a White Blood Cell (WBC) count of < 3,500/mm^3. The risk of agranulocytosis is highest in the first 3 months of clozapine treatment, and 95 percent of the cases occur within the first 6 months (Young et al, 1998; Ojoung & Allen, 2013). Patients treated with Clozapine in the UK and United States for a psychiatric or motion disorder must register themselves with the Clozapine Patient Monitoring Services (CPMS) to ensure that no patient can receive the drug without a recent satisfactory hematological result (Patterson, et al., 2010). Blood serum must be within normal range (RBC 45%, Plasma 55% and Buffy coat 1%) (Pies, 2005). If a patient experiences a sharp decline in their white blood cell count, they are to immediately discontinue the drug and a hematologist should be consulted immediately (Young et al., 1998; Ojoung & Allen, 2013).

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