Psychiatria Danubina, 2023; Vol. 35, Suppl. 2, pp 66-71
Conference paper

Review

ASSOCIATION BETWEEN BIPOLAR DISORDER AND PARKINSON'S DISEASE

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SUMMARY

Bipolar disorder and Parkinson's disease are two distinct neurological conditions that share common features related to dopaminergic dysfunction. This article presents a comprehensive review of the existing literature to investigate the association between bipolar disorder and Parkinson's disease, focusing on the dopaminergic hypothesis and potential therapeutic options.

The dopaminergic hypothesis suggests that both bipolar disorder and Parkinson's disease involve impairments in the nigrostriatal or mesolimbic dopaminergic pathways. Studies have demonstrated alterations in dopamine regulation during manic and depressive phases of bipolar disorder. Similarly, Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra, resulting in motor symptoms.

Recent analyses have highlighted a predisposition to Parkinson's disease in individuals with bipolar disorder. Longitudinal studies and meta-analyses have demonstrated an increased risk of developing Parkinson's disease in patients with bipolar disorder. However, differentiating idiopathic Parkinson's disease from parkinsonism induced by medications used in bipolar disorder can be challenging. Dopamine transporter (DAT) scans can aid in making a differential diagnosis.

Treatment options for patients with both bipolar disorder and Parkinson's disease are limited. Neuroleptics, commonly used to manage psychotic symptoms in Parkinson's disease, may worsen motor symptoms and have limitations in bipolar disorder patients. Clozapine has shown efficacy in treating psychosis without worsening motor symptoms. Pimavanserin, an inverse agonist of the 5-HT2A receptor can offer new opportunities.

However, its efficacy in bipolar disorder patients with Parkinson's disease remains unexplored.

In conclusion, the association between bipolar disorder and Parkinson's disease is supported by the involvement of the dopaminergic system in both conditions. The identification of shared mechanisms opens new avenues for potential therapeutic interventions. Further research is needed to investigate the efficacy of pimavanserin and explore other treatment options for individuals with both bipolar disorder and Parkinson's disease.

Key words: *bipolar disorder - Parkinson disease – dopamine - neurotransmitter imbalance - therapeutics*

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INTRODUCTION

Bipolar disorder is a chronic mood disorder that typically develops around the age of 20. This disorder is characterized by chronic episodes of mania in bipolar disorder type I and hypomania in bipolar disorder type II, as well as episodes of depression (Grande et al. 2016a, Murray et al. 1997). The estimated prevalence of bipolar disorder in the general population is 2.4%. The etiology of bipolar disorder is not clearly established, but it is likely to involve multifactorial causes. Genetic risk factors have been identified through studies of monozygotic twins, as well as environmental risk factors such as viral infections during childhood or childhood maltreatment (Kim et al. 2015, Bortolato et al. 2017).

Numerous studies have highlighted the involvement of the dopaminergic system in both the manic and depressive phases of bipolar disorder (Berk et al. 2007).

The standard treatment for bipolar disorder typically involves the use of mood stabilizers such as lithium or antiepileptic drugs, as well as neuroleptics. However, these treatments can induce parkinsonism, which can be problematic for patients. Many patients experience improvement in their manic phase when taking neuroleptics that block dopaminergic receptors (Hilty et al. 1999). Additionally, many patients with Parkinson’s disease experience hypomanic episodes when receiving Levodopa, a dopaminergic agonist (Murphy et al. 1971).

Parkinson's disease is one of the major neurodegenerative diseases, with a prevalence of 1% in individuals over the age of 60, second only to Alzheimer's disease (de Lau & Breteler 2006). Parkinson's disease is primarily characterized by motor symptoms such as rigidity, bradykinesia, and resting tremor, which have a negative impact on patients’ social life. Several genetic studies have attempted to identify mutations, but the results have been somewhat disappointing, and it is generally accepted that Parkinson's disease is primarily idiopathic (Jankovic & Tolosa 2007). Motor symptoms are related to the loss of dopaminergic neurons, although the exact explanation is unclear.

In addition to these motor symptoms, patients with Parkinson's disease often experience psychiatric symptoms, including depression, anxiety, insomnia, cognitive and behavioral changes, and even episodes of psychosis (Aarsland et al. 2009). Depressive episodes are associated with Parkinson's disease and can even

be present before the onset of motor symptoms. Research shows that depression and its severity increase the risk of developing Parkinson's disease (Gustafsson et al. 2015).

Recent meta-analyse and longitudinal study on large cohorts have also demonstrated an increased risk of Parkinson's disease in individuals with bipolar disorder (Faustino et al. 2021, Huang et al. 2019). However, little data is available on the association between these two comorbidities, and therapeutic options for patients with both diseases are limited, making the management of these patients challenging.

METHODOLOGY

For this article, a literature review was conducted using PubMed with the following keywords: Bipolar disorder, Parkinson's disease, Parkinsonism, Mood disorder. Studies with peer reviews were given priority.

THE DOPAMINERGIC HYPOTHESIS

Dopamine dysfunction is involved in both conditions. There would be a concomitant impairment in the two disorders of the nigrostriatal and mesolimbic dopaminergic pathways.

The dopaminergic hypothesis of bipolar disorder dates back to the 1970s. It emerged following the observation of manic episodes triggered by amphetamine use and the antimanic action of neuroleptics. The alternation of manic and depressive phases has been associated with alternations of hyperdopaminergia and hypodopaminergia due to a homeostatic imbalance (Ashok et al. 2017). In bipolar disorders, a decrease in dopaminergic regulation can be observed during the depressive phase, which is compensated for by the manic phase. This overall leads to a dopaminergic environment. For decades, neuroleptics have proven effective in treating manic phases through their actions on D2/D3 receptors, although they were initially used for schizophrenia. Moreover, some neuroleptics have also been found to be effective in treating depression in bipolar patients, with long-term benefits in stabilizing the disorder.

Other studies have also supported this hypothesis through imaging techniques, revealing increased D2/D3 receptor availability in patients during the manic phase.

The pathophysiological mechanism of Parkinson's disease involves depigmentation of the substantia nigra and locus coeruleus, with neuronal loss in the substantia nigra's pars compacta. Apoptosis and autophagy processes are involved in this process, leading to irreversible loss of dopamine-producing cells. Other areas are also affected, such as the basal nucleus of Meynert and the dorsal motor nucleus of the vagus nerve. Lewy bodies can also be found in certain areas. The reasons for these neurodegenerative processes are not clear. The dopamine pathway has a direct implication in medication, as dopaminergic agonists play a predominant role (Hayes 2020).

Levodopa is one of the commonly prescribed treatments and is highly effective in alleviating symptoms without affecting the progression of the disease. It is a precursor to dopamine that can cross the blood-brain barrier, allowing the remaining dopaminergic neurons to produce more dopamine and alleviate the symptoms. Carbidopa is also used to block the metabolism of levodopa in the periphery, increasing its bioavailability in the central nervous system. Dopaminergic agonists are also used to stimulate dopaminergic receptors.

However, the pathophysiological mechanisms are more complex, and other pathways, such as the serotonergic and glutamatergic pathways, are also considered (Grande 2016b). The inflammatory pathway is also studied in several articles, as chronic inflammation is a significant contributing factor to substantia nigra loss in Parkinson's disease. This inflammatory pathway is also found in studies related to bipolar disorder, showing an increase in TNF-alpha and IL-6 levels during depressive and manic phases (Saccaro et al. 2020).

BIPOLAR DISORDER PREDISPOSES TO PARKINSON'S DISEASE

Two recent analyses highlight a predisposition to Parkinson's disease in patients with bipolar disorder. Huang et al.'s study utilizes the Taiwan National Health Insurance Research database, which covers 23 million residents of Taiwan, representing 99% of the population. This longitudinal study shows that patients diagnosed with bipolar disorder between 2001 and 2009 have an increased risk of being diagnosed with Parkinson's disease during the follow-up period. The study followed 56,340 patients with bipolar disorder who were compared to 225,360 control patients. The study also emphasizes that a greater number of hospitalizations and more severe decompensations are associated with a higher risk of subsequently developing Parkinson's disease.

Faustino et al.'s meta-analysis includes seven studies involving 4,374,211 participants. This study demonstrates a three-fold increased risk of developing Parkinson's disease in individuals with preexisting bipolar disorder. However, this meta-analysis has some limitations as some of the studies included do not differentiate between idiopathic Parkinson's disease and drug-induced parkinsonism. Consequently, some patients may receive an incorrect diagnosis of Parkinson's disease. This can be attributed to the fact that medications used in bipolar disorder, such as lithium, neuroleptics, and antiepileptics, can cause drug-induced parkinsonism (Factor et al. 2019). Thus, studies

may present an overdiagnosis of idiopathic Parkinson's disease based on the diagnostic criteria used (Fazio et al. 2018). Nonetheless, it is important to note that certain parkinsonian characteristics may not necessarily be linked to medication use, and further clarification is necessary.

Clinically differentiating idiopathic Parkinson's disease from parkinsonism can be challenging; however, the distinction is crucial. To differentiate between these two conditions, a DAT-Scan is necessary. The DAT-Scan is a brain scintigraphy that assesses dopamine metabolism in the brain. It can particularly reveal denervation of the dopamine pathways in the basal ganglia in Parkinson's disease. Parkinson's disease results from decreased striatal dopamine production and manifests as parkinsonian symptoms when 60% to 80% of presynaptic dopaminergic neurons are lost. Dopamine transporter (DAT) proteins are used as biomarkers for Parkinson's disease, and their expression levels in the striatum can be evaluated using the commonly employed 123I-ioflupane and 123I-beta-CIT (Morbeillo et al. 2020).

Erro et al.'s study utilized SPECT-Scan to examine the dopaminergic nigrostriatal pathway in patients with bipolar disorder and parkinsonism (Erro et al. 2021). This allowed for a comparison of dopaminergic deficits in patients with Parkinson's disease and bipolar disorder with and without parkinsonism. The study revealed that 20% of patients with both bipolar disorder and parkinsonism exhibited an underlying dopaminergic deficit as measured by DAT-Scan. The bipolar disorder patients enrolled in this study did not exhibit clinical differences or medication use that could justify this discrepancy. This study emphasizes the importance of conducting DAT-Scans in such patients to determine differential diagnoses (Brigo et al. 2014).

Furthermore, this study opens the discussion on the etiology of this neurodegenerative process in patients with bipolar disorder. One of the main causes could be long-term use of neuroleptics. While many bipolar disorder patients achieve stabilization through neuroleptic treatment, some studies have reported the development of neurodegenerative parkinsonism in patients (Foubert et al. 2012) on long-term neuroleptic therapy. Studies also suggest a neurotoxic role of lithium (Lei et al. 2017). However, the study of Erro did not demonstrate differences in medication use between patients with degeneration of their dopaminergic circuitry and those without parkinsonism.

Another criticism has been raised regarding antiepileptic medications, which may exhibit neurotoxicity on the dopaminergic circuitry, as shown in Brugger et al.'s literature review (Brugger et al. 2016). Although the first case describing extrapyramidal symptoms related to valproate use was published by Lautin in 1979, subsequent cases reported in the literature have been highly heterogeneous (Lautin et al. 1979). Nevertheless, no differences in valproate use were observed between patient groups in Erro's study (Erro et al. 2021).

However, another hypothesis suggests a degenerative process due to neuroleptics, lithium, or antiepileptic medications (Erro et al. 2015). This hypothesis proposes that the medication's toxic effect on dopaminergic neurons leads to their cell death. Medication-induced parkinsonism is the second most common cause of parkinsonism after idiopathic Parkinson's disease (Lopez-Sendon et al. 2012). Generally, medication-induced parkinsonism resolves within six months after discontinuing the medication, but some patients continue to experience parkinsonism. A prospective study also demonstrated a link between exposure to neuroleptics and degenerative parkinsonism. Over a 15-year follow-up period, the risk of developing Parkinson's disease was found to be 3.2 times higher after exposure to neuroleptics, and only 30% of these cases developed Parkinson's disease during neuroleptic use (Foubert-Samier et al. 2012).

TREATMENTS FOR PARKINSON'S DISEASE AND BIPOLAR DISORDER

There are no precise guidelines for treating both bipolar disorder and Parkinson's disease, despite the significant therapeutic limitations presented by these two comorbidities. However, we can extrapolate from current knowledge. The use of neuroleptics in patients with Parkinson's disease extends beyond bipolar disorder or schizophrenia. Many Parkinson's disease patients develop psychotic symptoms as a result of their medication. Psychotic symptoms in Parkinson's disease, primarily manifesting as hallucinations and paranoid delusions, are present in nearly 40% of patients receiving dopamine replacement therapy (Factor et al. 2006).

Several studies have examined the appropriate medication for these psychotic symptoms. To counter these adverse symptoms, antipsychotics are regularly administered to patients. These act on the mesolimbic system at the level of D2 receptors (Romrell et al. 2003). Typical antipsychotics are not recommended for Parkinson's disease patients because doses that can block D2 receptors in the limbic system will also block D2 receptors in the dorsal striatum, leading to a decrease in the effectiveness of L-Dopa and motor symptoms.

Regarding atypical antipsychotics, studies have shown that even small doses of Risperidone or Olanzapine worsen motor symptoms, even at the minimum dosage required to treat psychotic symptoms (Weintraub & Stern 2005).

Clozapine is the only molecule that has demonstrated efficacy and tolerability in placebo-controlled

studies in patients with Parkinson's disease (Factor et al. 2001).

Studies have shown positive results with relatively low doses ranging from 6 to 75 mg per day, which are much lower than the dosages used in schizophrenia-related psychoses. The hypothesis explaining its efficacy is that the dosage is not sufficient to block D2 receptors in the limbic system for a direct antipsychotic action. Its efficacy is thought to be related to its blocking action on the 5-HT2A serotonin receptor (Meltzer 1995). However, the use of clozapine in Parkinson's disease patients should be cautious due to its main side effects of sedation, hypotension, hypersalivation, and the risk of agranulocytosis.

Quetiapine may also be effective and has shown efficacy in open-label studies for psychosis without worsening motor symptoms, but it also has sedative and hypotensive effects that limit its tolerability (Merims et al. 2006). Moreover, double-blind, placebo-controlled studies have failed to demonstrate the efficacy of quetiapine compared to placebo in patients with Parkinson's disease and psychosis. The side effects of quetiapine and clozapine are mainly related to their action on the histamine H1 receptor and alpha 1 adrenoceptor blockade.

Some studies have also reported increased mortality in demented patients treated with neuroleptics, raising concerns about the use of these drugs in fragile patients (Ballard et al. 2009).

In addition to psychotic symptoms, a significant proportion of patients receiving dopaminergic agonists will experience manic or hypomanic episodes. Approximately 17% of Parkinson's disease patients will develop an episode when starting or increasing medication (Maier et al. 2014). Manic episodes have also been reported in patients undergoing deep brain stimulation (Temel et al. 2006). As mentioned below, choosing the appropriate neuroleptic treatment in patients in a manic phase with Parkinson's disease is challenging. Selecting the right mood stabilizer is also difficult due to their debilitating side effects. For example, lithium may induce postural and action tremors that can be difficult to tolerate in patients with Parkinson's disease, especially when they already experience resting tremors (Baek et al. 2014). Valproate also has limitations in use as it is associated with reversible parkinsonism (Zadikoff et al. 2007).

The development of pimavanserin and its FDA approval in 2016 offer new perspectives. Pimavanserin is an inverse agonist of the 5-HT2A receptor that has demonstrated antipsychotic action in animals. A study by Meltzer (Meltzer et al. 2010) demonstrated tolerability and safety in patients with Parkinson's disease. The molecule is reported to be more effective than placebo and improves hallucinations and delusions. Pimavanserin could be a new therapeutic option while avoiding the side effects of neuroleptics in patients with Parkinson's disease. Clinical trials are underway to study the efficacy of this molecule in other conditions such as schizophrenia and major depressive disorder. However, no study has yet examined the utility of pimavanserin in patients with bipolar disorder and Parkinson's disease.

No studies have been conducted to investigate the efficacy of pimavanserin in bipolar patients with Parkinson's disease, and its use is currently off-label. A study published in late 2022 by Chesika Judyth Crump et al. (2022) presented three clinical cases showing stable mood maintenance in patients receiving pimavanserin instead of other neuroleptics. However, large-scale controlled studies are needed to confirm the effectiveness of this treatment. Furthermore, a recent placebo-controlled, randomized phase 2 study is currently investigating the addition of pimavanserin to antidepressants in patients with major depressive episodes with inadequate response. This study reportedly showed a significant improvement in depressive symptoms (Fava et al. 2019). This opens up possibilities for the utility of pimavanserin in mood disorders.

CONCLUSION

Bipolar disorder and Parkinson's disease are two associated conditions, not only due to the increased risk of Parkinson's disease in individuals with bipolar disorder but also due to the neurotransmitters involved. The dopaminergic pathway is currently highlighted in various studies, although the explanation is not clear. Medication used for one condition can lead to features resembling the other condition. Treating both diseases simultaneously without exacerbating symptoms of the other disease proves to be very challenging and limited. Currently, there are no precise guidelines for such cases despite the association between these two pathologies. Although clozapine and quetiapine are currently recommended, new prospects are available to patients with pimavanserin, which may prove its efficacy due to its unique mechanism of action. Future studies should attempt to understand the underlying mechanism associating these two conditions and establish clear treatment recommendations for these patients.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

Contribution of individual authors:

Romain Geelhand de Merxem: manuscript writing.
Sandrine Launay & Catherine Hanak: proofreading.

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