Long-Term Care Updates

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Treating psychosis in Parkinson's disease: a comprehensive approach

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Introduction

Parkinson's disease (PD) is a chronic and progressive neurological disorder caused by a decline in dopamine production, a critical neurotransmitter in the brain. It is primarily recognized by key motor symptoms of resting tremors, muscle rigidity, slowness or absence of movement, and balance and posture instability. Beyond its well-known motor symptoms, PD also has a range of nonmotor features, including Parkinson's disease psychosis (PDP). This is a complex and often distressing condition characterized by hallucinations, delusions, and altered reality in patients with PD, particularly in advanced stages. It affects a significant proportion of PD patients, with prevalence rates estimated to range from 18% to 50%.[1] Risk factors for PDP include high doses of anti-parkinson drugs, presence of dementia, advancing age, impaired vision, depression, presence of sleep disorders, high comorbid disease burden, and longer disease duration. The impact on patients is profound, leading to reduced quality of life, as well as an increased burden on caregivers and health care resources.[2] Addressing PDP requires a multifaceted treatment approach that balances managing psychotic symptoms with preserving motor function.

Non-Pharmacological Approaches

The initial steps in treating PDP often involve non-pharmacologic interventions that focus on addressing potential underlying contributors and providing support. Reassurance and emotional support for patients experiencing psychosis can mitigate fear and anxiety. Creating a stable and predictable environment by reducing noise and optimizing lighting can decrease sensory triggers that exacerbate psychotic episodes. Equipping caregivers with the knowledge and skills to manage psychosis is also crucial. This includes understanding the condition, recognizing triggers, and providing reassurance during episodes of hallucination or delusions.[3]

Novel Drug Approvals (November 2024)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Attruby	Acoramidis	Cardiomyopathy	Transthyretin stabilizer	Oral tablets
Rapiblyk	Landiolol	Supraventricular tachycardia	Beta-blocker	Intravenous injection
Revuforj	Revumenib	Relapsed or refractory acute leukemia	Menin inhibitor	Oral tablets
Ziihera	Zanidatamab-hrii	Biliary tract cancer	Bispecific HER2-directed antibody	Intravenous injection

Certain reversible factors can worsen psychosis in PD, and addressing these should be a priority. Conditions such as urinary tract infections (UTIs), dehydration, or metabolic imbalances should be ruled out and corrected when possible. In addition, assessing for dementia, which frequently coexists with PDP, is essential since it can amplify psychotic symptoms.[4]

Optimizing Current Medications

Pharmacologic triggers, particularly dopaminergic medications used to manage motor symptoms, are often implicated in PDP. Stopping all potentially offending medications is usually not an option; however, these medications can be reduced or discontinued in an order that balances potency and exacerbation of hallucinations with preserving motor function. If a temporal relationship is unclear, the suggested sequence begins with reducing or discontinuing anticholinergics. Medications like benztropine and trihexyphenidyl can exacerbate confusion and hallucinations in elderly patients. Next, it is recommended to taper or stop amantadine, dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, or catechol-O-methyltransferase (COMT) inhibitors. Finally, if symptoms persist, adjusting the dose of levodopa may be a last resort. This should be done very cautiously to avoid worsening motor symptoms. Abrupt changes in PD medication should always be avoided to prevent withdrawal syndromes or motor deterioration.[4]

Pharmacologic Treatment

When psychotic symptoms persist despite optimizing PD medications, additional pharmacologic treatment may be necessary. Preferred agents include pimavanserin, quetiapine and clozapine. Other first or second-generation antipsychotics, such as haloperidol, risperidone, or olanzapine, should generally be avoided as they block dopamine and can significantly worsen PD motor symptoms.[5]

Pimavanserin is a selective serotonin 5-HT2A inverse agonist specifically approved for PDP. In clinical trials, it led to a 3-point improvement over 6 weeks versus placebo using the 45-point PD-adapted scale for assessment of positive symptoms without impairing motor function.[6] The recommended dose is 34mg orally once daily without titration but can be reduced to 10mg once daily in patients also taking strong cytochrome P450 3A4 inhibitors. Pimavanserin should be avoided in patients with known QT prolongation, those taking drugs known to prolong the QT interval, and those with a history of cardiac arrhythmias or other conditions that may increase the risk of torsade de pointes. The most common potential side effects are peripheral edema, nausea, and constipation.[7]

Quetiapine is an atypical antipsychotic that can also be used off-label for PDP due to its lower dopamine receptor-blocking effects; however, evidence regarding its efficacy is mixed. In various observational studies, approximately 80% of patients reported an improvement in symptoms. However, among five small placebo-controlled trials, only one demonstrated a significant advantage over placebo.[8] Despite the inconsistent data, it is still used often in practice. Typically, quetiapine is initiated at 12.5 to 25mg orally at bedtime and gradually increased based on response and tolerability up to 100mg. Because quetiapine can cause drowsiness, it can be helpful when taken at bedtime to improve exacerbations of confusion and psychosis with nightfall (sundowning) and target insomnia.[9] An additional morning dose can be added to control symptoms up to 200mg/day if needed. Other potential side effects besides sedation include orthostatic hypotension, QT prolongation, and metabolic changes (weight gain and hypercholesterolemia).[10]

Finally, clozapine is an antipsychotic with the ability to treat psychiatric symptoms in PD without worsening motor function. In the largest trial to date (n=60), mean scores on the Clinical Global Impressions scale were significantly improved compared to placebo and 25 patients recovered from delusions and hallucinations altogether.[11] It is initiated at 6.25mg a day orally in one or two divided doses. Clozapine can be increased based on response and tolerability every 3 to 7 days up to a maximum of 50mg/day. Despite being the first drug to show benefit in a double-blind, placebo-controlled trial, clozapine remains underutilized due to the Risk Evaluation and Mitigation Strategy (REMS) requirements of monitoring absolute neutrophil count because of the risk of agranulocytosis. Another important consideration is medication adherence. The risk of orthostatic hypotension is highest during clozapine's titration. If a patient misses therapy for one or more days, this medication must be reduced and re-titrated. Other potential side effects include weight gain, hypercholesterolemia, hyperglycemia, drowsiness, and constipation.[12]

Due to limited head-to-head comparisons between pimavanserin, quetiapine, and clozapine, treatment decisions should be individualized based on patient factors, cost, potential side effects, and provider judgment.

Comorbid conditions

Coexisting conditions can also exacerbate psychosis in PD and require targeted therapies. For example, in patients with concurrent dementia, cholinesterase inhibitors like rivastigmine or donepezil may be used to enhance cognitive function and reduce psychotic symptoms. These agents work by increasing acetylcholine levels, which can mitigate the cognitive and neuropsychiatric manifestations of Parkinson's-related dementia.[8] To address sleep disturbances in PD, melatonin, a naturally occurring hormone that regulates the sleep-wake cycle, may be used to manage insomnia and circadian rhythm disruptions. It is often preferred for its favorable safety profile, making it a suitable option for individuals seeking to improve sleep quality without the risk of excessive drowsiness.[8]

Conclusion

Treating PDP requires a delicate balance between alleviating psychotic symptoms and maintaining motor function. Regular assessments of both domains are essential to tailor the treatment plan effectively. By combining non-pharmacologic strategies, careful medication adjustments, and targeted pharmacologic therapies, healthcare providers can improve the quality of life for patients with PDP and their caregivers.

References

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