Long-Term Care Updates

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Update on pimavanserin use in treating psychosis

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Introduction

Psychosis is a frequent complication of Parkinson's Disease (PD) affecting more than 50% of Parkinson's patients at some time. Psychosis is characterized mainly by visual hallucinations and delusions. The adverse effects of antiparkinson medications, particularly dopamine agonists, are an important cause of psychosis. Current guidelines recommend reducing dopaminergic therapy and/or treating with an atypical antipsychotic, such as clozapine or quetiapine. However, atypical antipsychotics are often poorly tolerated due to side effects and lack major efficacy.[1]

Pimavanserin is a relatively new atypical antipsychotic and was the first medication approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of PD psychosis. Pimavanserin is a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity, and is indicated to treat hallucinations and delusions associated with PD psychosis.[2]

Approvals and Guidelines

Pimavanserin received FDA approval based on the results of a six-week, phase 3, randomized controlled trial studying its efficacy in treating PD psychosis. Cummings et al randomized 199 patients to receive either pimavanserin 40 mg daily or placebo. The primary outcome was measured as change in total SAPS-PD (Adapted Scale for the Assessment of Positive Symptoms in Parkinson's Disease) from baseline to day 43. A decrease in SAPS-PD indicated improvement. At the end of day 43, the SAPS-PD scores of the placebo versus pimavanserin group were -2.73 and -5.79 (95% CI, -4.91 to -1.20; p = 0.0014). Ultimately, pimavanserin was found to be superior to placebo for improving the positive psychotic symptoms (hallucinations, delusions), without worsening parkinsonism in patients with moderate to severe PD. Cummings et al also found pimavanserin to improve

daytime wakefulness, nighttime sleep quality, and caregiver burden. The adverse effects reported in the trial (hallucinations, falls, urinary tract infections) did not occur in the pimavanserin group at a rate significantly higher than placebo.[1] The Institute for Safe Medicine Practices (ISMP) criticized the approval of the drug in 2017 stating that it was based on limited scientific evidence and voiced concerns over the use of a non-validated measurement tool in the pivotal trial.[3]

Although no head-to-head trials have been conducted, a retrospective analysis of 676 patients prescribed either quetiapine, pimavanserin, or a combination of quetiapine and pimavanserin for the treatment of PD psychosis was published in 2018.[4] Prior to FDA approval of pimavanserin, atypical antipsychotics such as quetiapine or clozapine were commonly used to treat PD psychosis; however, these medications have also been associated with an increased risk of mortality. A retrospective matched-cohort study published in 2016 demonstrated a two-fold increased mortality risk during six months of antipsychotic use in patients with PD.[5] Moreno and colleagues sought to determine the relative mortality associated with pimavanserin versus an agent used in standard practice, quetiapine. The odds ratio for the quetiapine group of 1.74 (95% CI 1.15 to 2.62; n=505) demonstrated an increased risk of mortality as compared to the pimavanserin group's odds ratio of 1.23 (95% CI 0.57 to 2.68; n=113). The combination group had an odds ratio of 2.16 (95% CI 0.93 to 5.01; n=58). As the only significant increased mortality finding was in the quetiapine group, this study provided reassurance for providers and patients regarding the safety of pimavanserin use. However, the authors concluded that more research is needed to evaluate factors such as disease severity and cause of death.[4]

The Movement Disorders Society published an updated evidence-based review for treatment of non-motor symptoms in PD. The Society ultimately reviewed 37 new clinical studies to include in their recommendations. Pimavanserin was noted as efficacious and clinically useful in countries where it is available. Clozapine was additionally recognized as efficacious and clinically useful but requiring specialized monitoring. Quetiapine was not recognized as efficacious due to insufficient evidence, but the authors did list it as clinically useful. The Society mentioned a lack of safety data for pimavanserin beyond six weeks, but also cited the FDA's conclusion that the benefits of the drug still outweigh the risks. Despite this, practitioners should remain aware of the potential for QT prolongation and paradoxical worsening of symptoms.[6]

The American Geriatrics Society 2019 update to the BEERS criteria recognized pimavanserin as acceptable treatment in Parkinson's psychosis in patients aged 65 years and up. Pimavanserin, clozapine, and quetiapine were additionally listed as an exception to the general recommendation of avoidance of antipsychotics in PD.[7]

Investigative Indications

Although pimavanserin is only FDA approved for the treatment of hallucinations and delusions associated with PD psychosis, there are new indications under investigation.

A phase 2, multicenter, randomized, double-blind, placebo-controlled trial was conducted that assessed the safety and efficacy of pimavanserin as adjunctive treatment in patients with major depressive disorder (MDD) who had an inadequate response to therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI).[8] A total of 207 patients ≥18 years of age were randomized in a 3:1 ratio to receive either pimavanserin or placebo added to their current SSRI or SNRI regimen for 5 weeks (Stage 1). At the end of the 5 weeks, patients who were nonresponders to placebo were re-randomized in a 1:1 fashion to receive either pimavanserin or placebo for an additional 5 weeks (Stage 2). The researchers reported a significant improvement in the 17-item Hamilton Depression Rating Scale and the Sheehan Disability Scale in the pimavanserin group versus placebo at both Stages 1 and 2. Significant improvements with pimavanserin were also seen in some secondary endpoints including sexual functioning, daytime sleepiness, and mental health-related quality of life. The most common adverse effects reported in the pimavanserin group were dry mouth, nausea, and headache; all had an incidence <10%.[8]

Another phase 2, randomized, double-blind, placebo-controlled trial was completed that evaluated the efficacy of pimavanserin in patients with Alzheimer's disease psychosis.[9] This study was conducted in multiple nursing home sites in the United Kingdom and included 181 patients >50 years of age with possible or probable Alzheimer's disease and psychotic symptoms. Patients were randomized to receive either pimavanserin or placebo for 12 weeks. The primary outcome was the mean change in the Neuropsychiatric Inventory - Nursing Home Version (NPI-NH) psychosis score from baseline to week 6. A significant improvement was seen in the pimavanserin group versus the placebo group at week 6 (mean difference -1.84; 95% CI -3.64 to -0.04; p=0.045); however, this effect was not sustained at week 12. Upon subgroup analysis, it appeared that patients with more severe psychosis had an increased benefit. No significant differences in adverse events were noted between the two groups.[9]

A double-blind, placebo-controlled relapse prevention study of pimavanserin for the treatment of hallucinations and delusions associated with dementia related psychosis was recently completed. Results have not been published, but the study was designed to evaluate the use of pimavanserin in all-cause dementia to prevent the relapse of psychotic symptoms.[10,11]

Conclusion

Pimavanserin is the first atypical antipsychotic approved for the treatment of hallucinations and delusions related to PD psychosis. In the pivotal phase 3 randomized controlled trial, it was shown to improve hallucinations and delusions without worsening Parkinson's. Pimavanserin is recognized by both the BEERS list and Movement Disorders Society as efficacious in treatment for PD psychosis. Preliminary trials have been conducted investigating the use of pimavanserin for treatment of psychosis from other causes; however, further research is necessary before it can be recommended for these indications.

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