Pimavanserin is not curative, but can improve the quality of life remaining for the person with Parkinson’s disease who typically has been suffering from this relentless neurodegenerative disease for years. Using pimavanserin effectively requires knowledge not only about the product itself, but also about the treatments pimavanserin is replacing.

An older description of the clinical features of Parkinson’s disease reads:

Late in the illness, about 10 percent of patients, especially those with dementia, develop psychotic episodes. These episodes are often precipitated by medications and are associated with the physical manifestations of excessive dopamine activity, such as dyskinesias. In treating such psychosis, the first step is to reduce the antiparkinson medication, especially the nighttime doses. Minor tranquilizers then might be given. Although neuroleptics are often necessary, the concurrent use of L-dopa and dopamine antagonist neuroleptics should be avoided.1 (p. 323)

Such was the state of the art in 1985 when I was in the middle of my training in psychiatry.

Important advances in our knowledge have been made since then. There is now a better appreciation of the pathophysiology of Parkinson’s disease (PD), including the non-motor symptoms that can predate the first evidence of motor abnormalities by 2 decades,2 as well as acknowledgment that psychotic symptoms can emerge in almost half of patients with PD and that psychotic symptoms are not necessarily related to dopaminergic or anticholinergic medications.3,4 Intriguing hypotheses have emerged suggesting that PD may start in the peripheral nerves in the gut and spread to the central nervous system through the vagus nerve via prion-like mechanisms, known as the Braak hypothesis, as suggested by a lower risk for PD in individuals who have undergone vagotomy.5 In the clinic, the availability of second-generation antipsychotics with the potential to ameliorate psychosis without aggravating the motor symptoms of PD has been a significant achievement, although their use has been limited by concerns over special monitoring (clozapine), insufficient evidence for efficacy (quetiapine, as tested in controlled trials), or unacceptable tolerability (olanzapine, also as tested in controlled trials).6,7 Pimavanserin, a selective serotonin 5-HT2A receptor inverse agonist/antagonist with no appreciable affinity for dopaminergic receptors, was approved in the US in 2016 specifically for the treatment of Parkinson’s disease psychosis (PDP). Pimavanserin has demonstrated efficacy in reducing psychotic symptoms, does not need special monitoring as required for clozapine, and can be given alongside medications being used to manage the commonly disabling motor symptoms of PD without making them worse.8 Pimavanserin is not curative, but can improve the quality of life remaining for the person with PD who typically has been suffering from this relentless neurodegenerative disease for years.

Using pimavanserin effectively requires knowledge not only about the product itself, but also about the treatments pimavanserin is replacing.
treatments pimavanserin is replacing. Several analogies exist regarding this. For example, using suvorexant (an orexin receptor antagonist) to manage insomnia requires knowing that it has no cross-tolerance to classic hypnotics; if the older hypnotic is stopped abruptly, withdrawal symptoms and rebound phenomena can emerge, and the prescriber (and patient) will likely blame the new agent for these problems and summarily declare suvorexant ineffective.

Thus, guidance for switching from “off-label” antipsychotics to “on-label” pimavanserin for PDP is welcome.9 The authors espouse several general principles for treating PDP: avoiding dopamine D2 receptor antagonism (which worsens the motor symptoms of PD), maintaining a stable level of serotonin 5-HT2A receptor antagonism during the transition (this is the desirable pharmacodynamic property that should be continued), and avoiding rebound effects when discontinuing agents with anticholinergic and antihistaminergic actions (such as clozapine and quetiapine). Abrupt discontinuation of antipsychotic drugs is known to cause both withdrawal and rebound effects, including withdrawal dyskinesias, rebound psychosis, anxiety, agitation, and insomnia, and autonomic symptoms such as sweating, tremor, diarrhea, and other gastrointestinal symptoms. The current dose of the agent to be discontinued will determine the duration of the taper needed, but there can be considerable individual variation among patients. The authors of the guidance wisely note that “reducing the quetiapine before the pimavanserin has started to work may cause the patient to deteriorate during the switch. This can be avoided by waiting to taper quetiapine for 4 to 6 weeks after starting pimavanserin.”9

If sufficient care is not taken when switching, the new medication gets blamed for all ills. The figures provided in the guidance illustrate best practices clearly and concisely.

Once on pimavanserin, what can an individual expect? The 6-week pivotal clinical trial that led to the approval of pimavanserin for PDP evidenced a difference of 3.06 points between pimavanserin 34 mg/d and placebo on the Parkinson’s disease–adapted scale for assessment of positive symptoms (SAPS-PD).10 It has been calculated that a 2.33-point change on the SAPS-PD corresponds to a clinically meaningful 1-unit change on the Clinical Global Impressions–Improvement scale (a 7-point scale where 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse).11 Thus, on average this minimal threshold has been met. However, the big question is what are the chances of a more robust response? Moreover, what are the chances of stopping because of adverse effects? Clinically intuitive effect sizes such as number needed to treat (NNT) and number needed to harm (NNH) can help describe these study outcomes.12,13 About 70% of persons receiving pimavanserin 34 mg/d experienced a ≥3-point decrease from baseline on the SAPS-PD, compared with about 40% for those receiving placebo; NNT for a ≥3-point decrease from baseline on the SAPS–PD for pimavanserin 34 mg/d versus placebo is 4, meaning for every 4 persons randomized to pimavanserin rather than placebo, one would expect one additional responder with a ≥3-point decrease.14 This is not different from other psychiatric interventions for other disorders, and places pimavanserin as a mainstream treatment with regard to efficacy. A score of 1 on the CGI-I (ie, very much improved) was achieved by 20% of patients receiving pimavanserin (and 7% of those receiving placebo), resulting in a NNT versus placebo of 8. A 100% decrease from baseline on the SAPS-PD (elimination of all symptoms) was achieved by 14% of patients receiving pimavanserin (and 1% of those receiving placebo), resulting in a NNT of 8 for this highly desirable outcome. Discontinuation rates due to adverse events were low. The NNH is 21 for the overall tolerability metric of discontinuation because of an adverse event for pimavanserin 34 mg/d versus placebo as observed in the available studies. Likelihood to be helped or harmed (LHH) can also be calculated and describes how more likely one can expect a positive effect versus a problem.13 When comparing a ≥3-point decrease from baseline on the SAPS-PD versus discontinuation because of an adverse event, the LHH is about 5. This can be interpreted as pimavanserin 34 mg/d is about 5 times more likely to result in a response than having to stop because of an adverse event. Given that efficacy is expected to be observable within 6 weeks, a trial of pimavanserin appears compelling. Now we have some explicit guidance on how to go about it.

Disclosures

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REFERENCES:

3. Fénelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson’s disease–associated psychosis: a cross-