



# Guidance for switching from off-label antipsychotics to pimavanserin for Parkinson's disease psychosis: an expert consensus

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Patients with Parkinson's disease psychosis (PDP) are often treated with an atypical antipsychotic, especially quetiapine or clozapine, but side effects, lack of sufficient efficacy, or both may motivate a switch to pimavanserin, the first medication approved for management of PDP. How best to implement a switch to pimavanserin has not been clear, as there are no controlled trials or case series in the literature to provide guidance. An abrupt switch may interrupt partially effective treatment or potentially trigger rebound effects from antipsychotic withdrawal, whereas cross-taper involves potential drug interactions. A panel of experts drew from published data, their experience treating PDP, lessons from switching antipsychotic drugs in other populations, and the pharmacology of the relevant drugs, to establish consensus recommendations. The panel concluded that patients with PDP can be safely and effectively switched from atypical antipsychotics used off label in PDP to the recently approved pimavanserin by considering each agent's pharmacokinetics and pharmacodynamics, receptor interactions, and the clinical reason for switching (efficacy or adverse events). Final recommendations are that such a switch should aim to maintain adequate 5-HT<sub>2A</sub> antagonism during the switch, thus providing a stable transition so that efficacy is maintained. Specifically, the consensus recommendation is to add pimavanserin at the full recommended daily dose (34 mg) for 2–6 weeks in most patients before beginning to taper and discontinue quetiapine or clozapine over several days to weeks. Further details are provided for this recommendation, as well as for special clinical circumstances where switching may need to proceed more rapidly.

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**NbN-2 compliant keywords:**

- pimavanserin: serotonin receptor inverse agonist/antagonist (5-HT<sub>2A</sub>)
- clozapine: dopamine receptor antagonist (D<sub>2</sub>), serotonin receptor antagonist (5-HT<sub>2</sub>), norepinephrine receptor antagonist ( $\alpha$ 2)
- quetiapine: dopamine receptor antagonist (D<sub>2</sub>), serotonin receptor antagonist (5-HT<sub>2</sub>), norepinephrine reuptake inhibitor (metabolite)









**Introduction**

Parkinson's disease psychosis (PDP) is an increasingly recognized nonmotor aspect of Parkinson's disease (PD).<sup>1,2</sup> Prior to 2016, recommendations for treating PDP focused primarily on off-label use of clozapine and quetiapine.<sup>3,4</sup> Randomized, controlled trials demonstrated efficacy for clozapine at low doses (6.25 mg–50.0 mg/d) with limited adverse motor effects. Quetiapine failed to demonstrate clear efficacy in at least 4 of 5 clinical trials, but also had limited impact on motor function, and was very commonly prescribed in PDP.<sup>5,6</sup> The limited impact of these drugs on PD motor

symptoms may be attributed to the fact that both are weak D<sub>2</sub> receptor antagonists. Both are also antagonists at serotonin 2A (5-HT<sub>2A</sub>) receptors, clozapine more potently than quetiapine (see Table 1), which may contribute to efficacy.<sup>7</sup> Other antipsychotics that are potent D<sub>2</sub> antagonists or partial agonists generally produce intolerable adverse motor effects and are not recommended for PDP.<sup>8–10</sup>

In 2016, the US FDA approved the first drug for treatment of psychotic symptoms in PDP.<sup>11</sup> Pimavanserin is a selective 5-HT<sub>2A</sub> receptor inverse agonist/antagonist with no appreciable affinity for dopaminergic receptors,<sup>12–14</sup> it exerts clinically significant antipsychotic effects without impact on motor symptoms.<sup>15–18</sup> Since the introduction of pimavanserin to the market, switching a PDP patient from a previous antipsychotic to pimavanserin is a common clinical consideration, motivated perhaps by lack of efficacy or side effect concerns with the previous agent. However, the details of how to implement such a switch have not been clear. An abrupt switch involves stopping a drug that may have provided partial benefit, potentially causing an interval of worsening psychosis or rebound insomnia before pimavanserin's

**TABLE 1. Receptor binding affinities for selected antipsychotic agents<sup>46</sup>**

Drug	 D <sub>2</sub>	 5HT <sub>1A</sub>	 5HT <sub>2A</sub>	 $\alpha$ <sub>1A</sub>	 $\alpha$ <sub>2C</sub>	 M <sub>1</sub> (central)	 M <sub>2-4</sub> (peripheral)	 H <sub>1</sub>
Pimavanserin	-	-	++++	-	-	-	-	-
Haloperidol	++++	-	++	++	++	-	-	-
Clozapine	++	-	+++	+++	++	++	+++	++++
Olanzapine	+++	-	+++	+	-	++	+	+++
Quetiapine	++	-	+	-	-	+	+	+++
Risperidone	++++	-	++++	+++	++	-	-	++
<b>Effects of blockade</b>	Antipsychotic, antimanic, anti aggression, EPS/akathisia, tardive dyskinesia, increased prolactin	Anxiolytic, antidepressant, anti-EPS/akathisia	Anti-EPS/akathisia, antipsychotic	Postural hypotension, dizziness, syncope	Antidepressant, increased alertness, increased blood pressure	Memory, cognition, dry mouth, anti-EPS/akathisia	Blurred vision, constipation, urinary retention, tachycardia, hypertension	Anxiolytic, sedation, sleep induction, weight gain, anti-EPS/akathisia
<b>Potential withdrawal/rebound effects</b>	Psychosis, mania, agitation, akathisia, withdrawal, dyskinesia	Anxiety, EPS/akathisia	EPS/akathisia, psychosis	Tachycardia, hypertension	Hypotension	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia	Diarrhea, sweating, nausea, vomiting, bradycardia, hypotension, syncope	Anxiety, agitation, insomnia, restlessness, EPS/akathisia

+ weak binding affinity (100 > Ki < 1000); ++ moderate binding affinity (10 > Ki < 100); +++ strong binding affinity (1 > Ki < 10); ++++ very strong binding affinity (Ki < 1); Abbreviations: 5-HT = serotonin;  $\alpha$  = adrenergic; D = dopamine; H = histamine; M = muscarinic. Ki (nM) values are derived from functional antagonist R-SAT™ assays (ACADIA, San Diego, CA, USA). “-” denotes no response. Adapted from Hacksell *et al.* *Neurochem Res* 2014; 39: 2008–2017 and from data on file.

**Box 1. Dosing Tips for Switching to Pimavanserin from Low Dose ( $\leq 100$  mg) Quetiapine (see Figure 3)**

- Add full dose (34 mg) pimavanserin to current low dose (up to 100 mg) quetiapine for 4 weeks.
- Allows pimavanserin to reach steady state and the duration of treatment necessary to reach its delayed onset of therapeutic action.
- Then reduce quetiapine by 50% weekly until reaching 12.5 mg, then discontinue.
- If efficacy for PDP diminishes during quetiapine taper, can return to previous dose level and try tapering again in 1 week.

**Box 2. Dosing Tips for Switching to Pimavanserin from High Dose ( $> 100$  mg) Quetiapine (see Figure 4)**

- Add full dose (34 mg) pimavanserin to current high dose ( $> 100$  mg) quetiapine for 4 weeks.
- Allows pimavanserin to reach steady state and the duration of treatment necessary to reach its delayed onset of therapeutic action.
- Then reduce quetiapine by 25% weekly until reaching 12.5 mg, then discontinue.
- If efficacy for PDP diminishes during quetiapine taper, can return to previous dose level and try tapering again in 1 week.

**Box 3. Dosing Tips for Switching to Pimavanserin from Low-Dose ( $\leq 100$  mg) Clozapine (see Figure 5)**

- Add full dose (34 mg) pimavanserin to continuing clozapine dose for 6 weeks.
- Then reduce clozapine by 6.25 mg weekly until discontinued and in no event, not less than 4 weeks of tapering.
- If efficacy for PDP diminishes during clozapine taper, can return to previous dose level and try tapering again in 1 week.
- Recommend not removing patient from clozapine registry for a few months in case clozapine must be restarted.

**Box 4. Dosing Tips for Switching to Pimavanserin from High-Dose ( $> 100$  mg) Clozapine (see Figure 6)**

- Add full dose (34 mg) pimavanserin to continuing clozapine dose for 6 weeks.
- Then reduce clozapine by 25 mg weekly until discontinued and in no event, not less than 4 weeks of tapering.
- If efficacy for PDP diminishes during clozapine taper, can return to previous dose level and try tapering again in 1 week.
- Recommend not removing patient from clozapine registry for a few months in case clozapine must be restarted.

expected onset of action. Cross tapering, on the other hand, can raise concerns about drug interactions or QTc prolongation due to the lack of data on combined therapy with pimavanserin. In the absence of controlled trials directly comparing these approaches, we here review relevant principles to consider and provide expert suggestions for how to switch patients from atypical antipsychotics to pimavanserin.

## Methods

A panel of 14 experts agreed to establish consensus recommendations aimed at identifying optimal strategies for switching from an off-label antipsychotic, especially quetiapine or clozapine, to pimavanserin for patients with PDP. Members of the group had expertise with PDP (including movement disorders neurologists and neuropsychiatrists) and with the receptor pharmacology of antipsychotics, collectively treating thousands of patients with PD and PDP, including more than 150

patients with pimavanserin. Twelve responded to a brief survey about their PDP treatment experience and preferences. This expert panel established the following objectives:

- To present the pharmacology of atypical antipsychotics as it relates to switching strategies
- To provide insights into current practice patterns and potential challenges associated with switching patients with PDP from atypical antipsychotics, especially quetiapine or clozapine, to pimavanserin
- To seek consensus on recommendations for best practices for how to switch patients to pimavanserin

This manuscript will review relevant antipsychotic pharmacology, published recommendations on switching antipsychotics in primary psychiatric illnesses,<sup>19,20</sup> and the pros and cons of various options from the perspective of substantial collective clinical experience. The manuscript was drafted by the authors, and all agreed to the final content.

## PDP Diagnosis

The first step in treating PDP is to verify the diagnosis. While definitions of PDP have differed over the years, a National Institute of Neurological Disorders and Stroke–National Institute of Mental Health working group proposed diagnostic criteria for PDP in 2007 that require at least 1 of the following: illusions, false sense of presence, hallucinations, or delusions. These features should not begin prior to the onset of PD motor symptoms, and should be present for at least 1 month, either as recurrent or continuous symptoms. Importantly, acute delirium and other medical, neurological, or psychiatric causes should be excluded.<sup>2</sup> Additionally, clinical judgment should be used in considering the need for treatment in patients with infrequent or non-bothersome symptoms.

## Treatment of PDP with Atypical Antipsychotics

Prior to 1990, medications for psychosis were limited to antidopaminergic agents.<sup>21</sup> However, administration of first-generation, or typical, antipsychotic drugs resulted in unacceptable exacerbation of motor symptoms due to the blockade of dopamine receptors. Therefore, these drugs and other strongly antidopaminergic treatments are generally not used to treat PDP, a recommendation supported by the Movement Disorder Society (MDS),<sup>22</sup> American Geriatrics Society,<sup>23</sup> and American Academy of Neurology.<sup>24</sup>

Between 1993 and 2003, several second-generation, or atypical, antipsychotic drugs were evaluated in patients with PDP. Although these agents have been approved as effective in the treatment of schizophrenia, they vary greatly in their pharmacokinetic (PhK) and pharmacodynamic (PhD) properties. For example, receptor binding profiles include differing affinities for an array of receptors types, including dopamine, serotonin, acetylcholine, histamine, and adrenergic receptors (Table 1). The differing PhK and PhD properties in general, and the potency in binding dopamine receptors in particular, lead to variable side effect profiles. Clinical experience has shown that drugs such as risperidone,<sup>25,26</sup> olanzapine,<sup>27,28</sup> aripiprazole,<sup>29</sup> and ziprasidone<sup>30,31</sup> may result in intolerable motor side effects for PD patients even at low doses, and therefore are widely considered to be poor choices for treatment of PDP. However, despite lacking a US Food and Drug Administration (FDA) indication for use in treating PDP, 2 of the atypical antipsychotics, clozapine and quetiapine, have frequently been used to manage the disorder.

Clozapine is an atypical antipsychotic drug with a complex pharmacology (Table 1). It is a potent antagonist at the H<sub>1</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>, and α<sub>1</sub> receptors; a

potent inverse agonist at the 5-HT<sub>2A</sub> receptors; and a relatively weak antagonist at the D<sub>2</sub> receptors. Inverse agonists are defined as drugs that, when bound to a receptor, produce the opposite intracellular effect as the endogenous ligand, even in the absence of the endogenous ligand. Pivotal clinical studies showed that clozapine improved PDP without substantially worsening parkinsonism.<sup>32–35</sup> However, clozapine carries the risk of neutropenia,<sup>36</sup> which requires frequent blood testing. The use of clozapine in PDP is also potentially further constrained by other limiting side effects, such as sedation, orthostatic hypotension, or anticholinergic effects including constipation.

Quetiapine, another atypical antipsychotic medication that has been evaluated in PDP, exerts potent antagonism at the H<sub>1</sub> receptor and relatively weaker binding at D<sub>2</sub> and 5-HT<sub>2A</sub> receptors (Table 1). Quetiapine showed lesser antipsychotic benefit than clozapine in some trials,<sup>37,38</sup> but did not differ significantly in another.<sup>35</sup> However, in 4 of 5 randomized controlled trials, quetiapine did not significantly reduce psychotic symptoms compared with placebo when objectively assessed using the Brief Psychotic Rating Scale.<sup>39–43</sup> The fifth study specifically excluded patients with delusions, and enrolled 16 patients, 5 of whom discontinued prematurely (including 4 of the 8 patients assigned to quetiapine). The treatment groups differed significantly only on secondary outcome measures.<sup>39</sup> In terms of safety, reported side effects in these studies included sedation, confusion, and orthostatic hypotension, which sometimes led to treatment discontinuation.<sup>39–43</sup> Among our panel, sedation was the quetiapine side effect that most commonly motivated a switch to pimavanserin (cited by all respondents), followed by hypotension (cited by two-thirds). Nevertheless, many experts continue to prescribe quetiapine in PDP, based in part on their clinical experience.<sup>44</sup> For instance, most of our expert panel reported that pimavanserin was their first-line medication for PDP, but one third chose quetiapine.

The *Evidence-Based Medicine Review* from the MDS, last published in 2011,<sup>22,24</sup> concluded that clozapine is efficacious for treating PDP with a safety risk that requires specialty monitoring, while quetiapine has an acceptable safety risk but may not be tolerated in this population at doses needed for benefit. Due to the monitoring requirements and safety risks of clozapine, and the lack of convincing efficacy associated with quetiapine, pimavanserin may be considered a first option for the treatment of PDP. A recent evidence-based review recommended pimavanserin and clozapine as first-line agents,<sup>45</sup> and the most recent American Academy of Neurology classification recommended pimavanserin and clozapine at level B, and quetiapine at level C.<sup>11</sup>

## Treatment of PDP with Pimavanserin

In 2016, pimavanserin (NUPLAZID<sup>®</sup>, ACADIA Pharmaceuticals Inc.) became the first drug approved by the FDA for the treatment of hallucinations and delusions associated with PDP.<sup>13</sup> Pimavanserin binds with high affinity to 5-HT<sub>2A</sub> receptors as an inverse agonist, with a 5-fold lower affinity to 5-HT<sub>2C</sub> receptors, and has no appreciable affinity for 5-HT<sub>2B</sub>, dopaminergic, muscarinic, histaminergic, or adrenergic receptors or for calcium channels.<sup>12,46</sup> An early phase 3 clinical trial with subjects randomized to placebo, 8.5, or 34 mg/d showed nonsignificant benefit for the highest dose (N=298), as did a trial with a maximum daily dose of 17 mg (N=123) and a small, ascending dose, phase 2 study (<https://clinicaltrials.gov/ct2/results?term=pimavanserin>).<sup>15,46</sup> The pivotal clinical trial was a randomized, double-blind, 2-arm, phase 3 study in 199 patients. It showed that pimavanserin 34 mg daily was significantly better than placebo at reducing frequency and/or severity of hallucinations and delusions in patients with PDP as measured using the Scale for the Assessment of Positive Symptoms–Parkinson's Disease (SAPS-PD,  $p=0.0014$ ) and the SAPS Hallucinations and Delusions subscales ( $p=0.0012$ ).<sup>16</sup> Sleep quality, caregiver burden, and other exploratory outcome measures also significantly improved with pimavanserin. Of course, treatment response varies; in the pivotal clinical trial, 68% of pimavanserin patients had a clinically meaningful response<sup>47</sup> (vs. 43% on placebo), 49% responded on the CGI-I (Clinical Global Impressions–Improvement) scale (vs. 26% on placebo), and partial response was typical (14% experienced a complete remission vs. 1% on placebo).<sup>16,48</sup> One quarter of our panel reported concern for breakthrough hallucinations or delusions as a reason for not switching some PDP patients to pimavanserin.

Importantly, pimavanserin did not worsen motor function compared with placebo, which is a major concern when treating PDP. Serious adverse events were uncommon in the clinical trials cited above, but the pimavanserin label shares with other drugs for psychosis a boxed warning of an increased risk of death in elderly patients with dementia.

## Initiating Pimavanserin in PDP Patients Not on an Antipsychotic

When the decision has been made to start a patient on pimavanserin, the recommended dose is 34 mg by mouth, once daily (Figure 1).<sup>13</sup> Given the long half-life of pimavanserin (approximately 57 hours), starting 34 mg immediately will likely produce a gradual increase in blood concentration over approximately 2 weeks. The only exceptions to the use of the 34 mg dose included in

the label are for patients who are taking strong inhibitors of cytochrome P450 (CYP) 3A4, in which case a 10 mg daily dose is recommended, and in patients taking CYP3A4 inducers, in whom “an increase in dosage may be needed.”<sup>13,49</sup> In the pivotal, randomized, placebo-controlled, phase 3 trial, a decrease in psychotic symptoms from baseline was evident at 2 weeks for pimavanserin and placebo. Improvement in the pimavanserin arm separated from placebo beginning at 4 weeks, with further improvement at 6 weeks.<sup>16</sup> The improvement at 6 weeks was significant and clinically meaningful.<sup>16</sup> This time to onset of therapeutic action is key to bear in mind when considering switching to pimavanserin, especially when switching from drugs like quetiapine or clozapine with much shorter half-lives. Efficacy of pimavanserin was maintained at 10 weeks during an open-label extension phase of the study.<sup>50</sup> Therefore, a minimum of a 6-week trial period with the 34 mg dose of pimavanserin is needed to fully assess efficacy.

## Pharmacologic Principles to Consider When Switching PDP Patients from an Antipsychotic to Pimavanserin

There are a number of factors that should be considered to increase success in antipsychotic switches, including PhK and PhD characteristics, receptor selectivity, reasons for the switch (efficacy or adverse events), and urgency of the switch. Although much of the data come from studies in other populations, abrupt discontinuation of antipsychotic drugs is known to cause both withdrawal and rebound effects (Table 2). The appearance of specific withdrawal symptoms depends on the target receptor. For example, abrupt withdrawal from antipsychotic drugs targeting dopamine D<sub>2</sub> receptors, 5-HT<sub>1A</sub>, and/or 5-HT<sub>2A</sub> receptors has been linked to withdrawal dyskinesias and rebound psychosis (Table 2), whereas abrupt withdrawal from drugs targeting histamine H<sub>1</sub> and muscarinic M<sub>1</sub> receptors has been linked to anxiety, agitation, and insomnia, and sometimes autonomic symptoms such as sweating, tremor, diarrhea, and other gastrointestinal symptoms (Table 2).<sup>7,20,51</sup> The potential for rebound and withdrawal phenomena is greatest when the pre- and post-switch antipsychotics differ considerably with regard to binding affinity for specific receptors, as these effects typically involve exposure of previously blocked receptors that are no longer targeted by the post-switch antipsychotic (PhD rebound). Differences in half-lives, time to steady state, and metabolism between pre- and post-switch antipsychotics (PhK rebound) may also contribute to rebound and withdrawal symptoms (Table 2), especially if loss of 5-HT<sub>2A</sub> receptor occupancy occurs in the transition between 2 drugs.<sup>51</sup> Withdrawal effects in

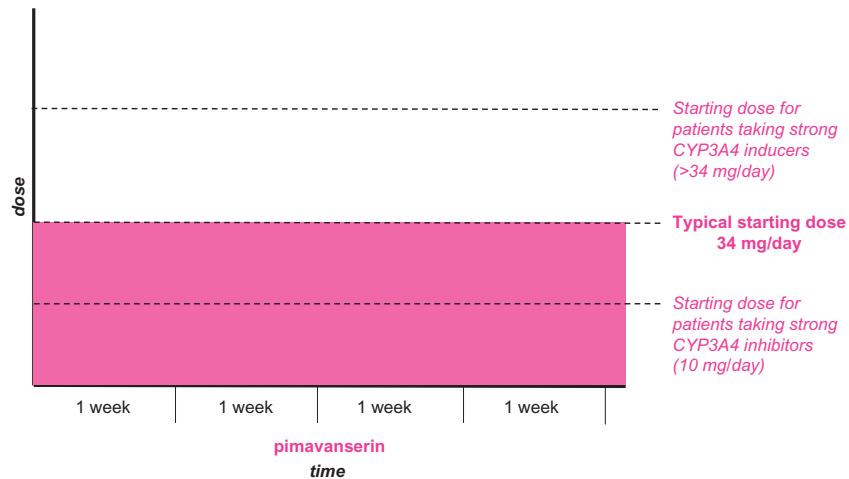


FIGURE 1. Patients not currently taking antipsychotic medication. Start full dose of pimavanserin immediately.

TABLE 2. Effects of blockade of receptors and potential side effects from withdrawal/rebound during switching

Receptor	Effects of blockade	Potential rebound/withdrawal effects
D <sub>2</sub>	Antipsychotic, antimanic, antiaggression, EPS/akathisia, tardive dyskinesia, increased prolactin	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
α <sub>1</sub>	Postural hypotension, dizziness, syncope	Tachycardia, hypertension
α <sub>2</sub>	Antidepressant, increased alertness, increased blood pressure	Hypotension
H <sub>1</sub>	Anxiolytic, sedation, sleep induction, weight gain, anti-EPS/akathisia	Anxiety, agitation, insomnia, restlessness, EPS/akathisia
M <sub>1</sub> (central)	Memory, cognition, dry mouth, anti-EPS/akathisia	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia
M <sub>2-4</sub> (peripheral)	Blurred vision, constipation, urinary retention, tachycardia, hypertension	Diarrhea, sweating, nausea, vomiting, bradycardia, hypotension, syncope
5-HT <sub>1A</sub> (partial agonism)	Anxiolytic, antidepressant, anti-EPS/akathisia	Anxiety, EPS/akathisia
5-HT <sub>2A</sub>	Anti-EPS/akathisia, antipsychotic	EPS/akathisia, psychosis

Abbreviations: 5-HT = serotonin; α, adrenergic; D = dopamine; EPS = extrapyramidal symptoms; H = histamine; M = muscarinic. Adapted from Correll 2010.<sup>51</sup>

general may be less severe when discontinuing the lower doses of quetiapine or clozapine typically prescribed to patients with PDP than when discontinuing the higher doses of antipsychotic drugs used in patients with schizophrenia.

### Potential Risk of Concomitant Therapy with Antipsychotics and Pimavanserin During Cross Taper

Pimavanserin is generally well tolerated with no worsening of motor function.<sup>15–17</sup> The safety profile of pimavanserin is consistent with its receptor pharmacology (Table 1) and differentiates this medication from current antipsychotic drugs. Based on the tolerability profile of pimavanserin, it is anticipated that there is a low risk of exacerbating the side effects of other antipsychotic medications when pimavanserin is administered concurrently. However, as with all drug combinations, clinicians should consider history of cardiac risk

factors and/or ECG data when pimavanserin is taken concurrently with other antipsychotics, as each carries a risk of modest (mean 5–8 msec) prolongation of the QTc interval.

### Recommendations: Switching to Pimavanserin in Patients Currently Taking an Antipsychotic with Suboptimal Efficacy and/or Tolerability

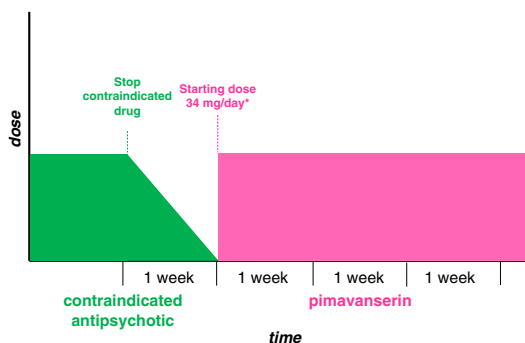
The goals of switching a patient with PDP from a current antipsychotic medication, especially quetiapine or clozapine, to pimavanserin are (1) to avoid dopamine D<sub>2</sub> antagonism, (2) to maintain a stable level of 5-HT<sub>2A</sub> antagonism during the transition so that efficacy is maintained throughout the switch, and (3) to avoid rebound effects whenever possible by monitoring the pharmacology of the medications involved, usually by slow down-titration of agents with anticholinergic and antihistaminic actions, such as quetiapine and clozapine.

Several principles should be considered when initiating pimavanserin in patients with PDP who are already taking an antipsychotic medication. Typical or atypical antipsychotic drugs with a high risk of motor side effects, such as haloperidol, risperidone, or olanzapine, are not recommended for patients with PDP, and these medications should be stopped as quickly as possible (Figure 2). Motor worsening may persist for 30 days, and often much longer, after these medications have been discontinued. Clozapine and quetiapine (at doses  $\leq 100$  mg) have a low propensity for worsening motor symptoms of PD.

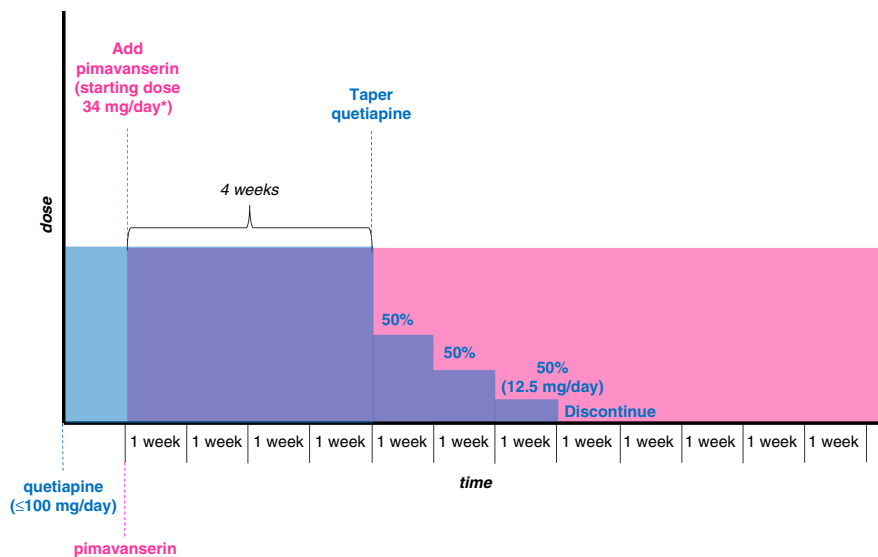
The nature, severity, and frequency of side effects and the current dose should always be considered before discontinuing medications. If one switches to pimavanserin because of the lack of efficacy with low-to-moderate doses of quetiapine ( $\leq 100$  mg/day), for most cases quetiapine may be tapered over 2–4 weeks starting 4–6 weeks after adding pimavanserin, with the goal of

minimizing rebound effects (eg, insomnia) and any loss of antipsychotic benefit that might occur from abrupt discontinuation of quetiapine (Box 1, Figure 3).<sup>7,51</sup> The duration of taper should depend on the current dose of quetiapine; in cases of treatment with quetiapine at  $>100$  mg/day, a longer period of down-titration of the quetiapine is suggested (Box 2, Figure 4). However, if a patient is experiencing sedation during the day that affects daily activities or increases the risk of falling, reducing or eliminating the daytime dose of quetiapine more abruptly may be considered. If, on the other hand, a patient is deriving a nocturnal sleep benefit from quetiapine due to sedation, removing the bedtime dose may worsen sleep and lead to an increase in psychotic symptoms. Given the low level of urgency for this type of switching, the authors recommend avoiding 2 changes in dosing at the same time (ie, increasing the new treatment while decreasing the older treatment) in order to reduce the risk of rebound agitation. Instead, it is recommended to allow the pimavanserin being initiated to attain the efficacy demonstrated at 4–6 weeks in controlled clinical trials prior to a slow down-titration of quetiapine over a few weeks. Persistent insomnia after withdrawal of quetiapine may require adjustments to this plan.

When switching from concomitant clozapine, for most cases, clozapine may be continued at the current dose for 6 weeks with pimavanserin 34 mg daily. At 6 weeks, total daily clozapine dose may be reduced by 6.25 mg to 25 mg weekly (Box 3, Figure 5), depending on the starting dose (eg, reduce by 25 mg if starting dose is  $>100$  mg/day) and physician preference (Box 4, Figure 6). Absolute neutrophil counts should be monitored for 2 weeks after clozapine discontinuation (see clozapine manufacturer prescribing information). The



**FIGURE 2.** Patients currently taking contraindicated antipsychotic. Stop as quickly as possible, then start pimavanserin after washout.



**FIGURE 3.** Patients currently taking quetiapine ( $\leq 100$  mg/day).

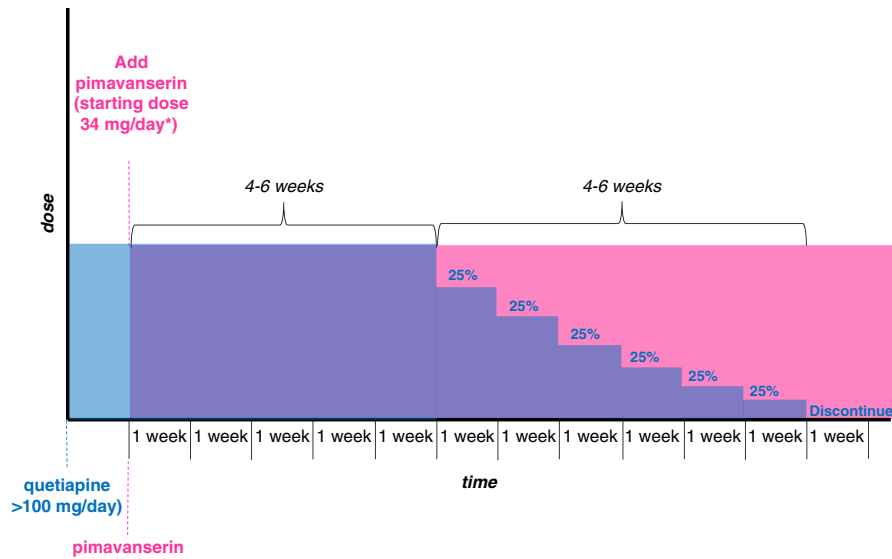


FIGURE 4. Patients currently taking quetiapine (>100 mg/day).

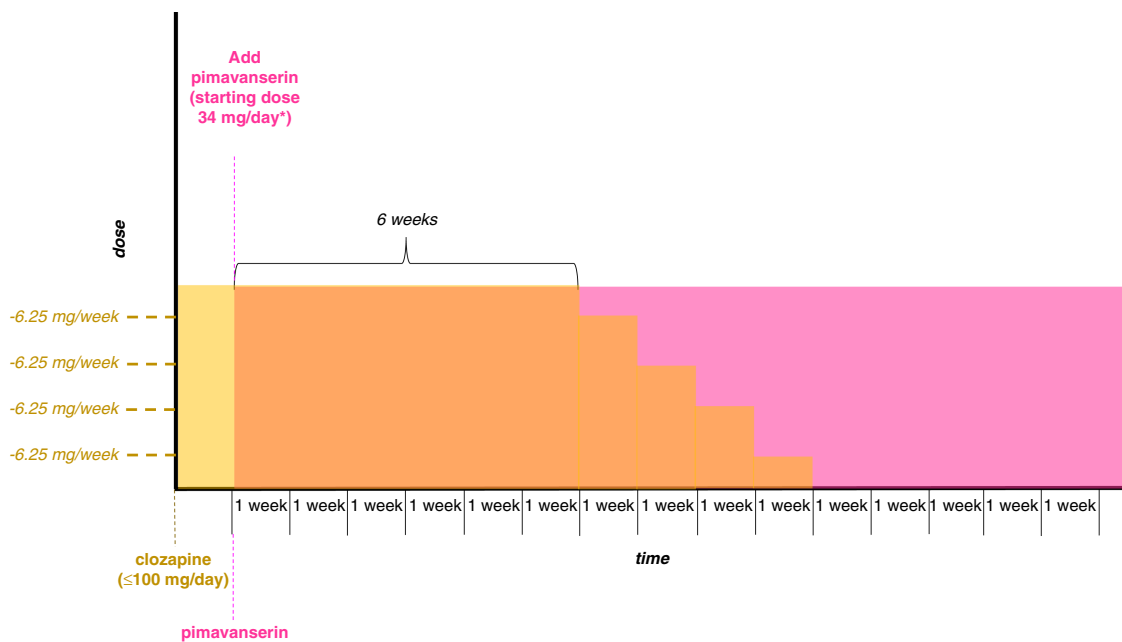


FIGURE 5. Patients currently taking clozapine ( $\leq 100$  mg/day).

patient may be continued in the clozapine registry for at least 2 months so that the patient will not have to be re-enrolled if clozapine is restarted.

As a general rule, if efficacy is reduced at any time during the down-titration of quetiapine or clozapine, return to the previous dose level and wait. Reduction can be attempted again after 1 week, or if added benefit of the combined therapy is clear, the patient may need to continue both medications.

## Conclusions

Antipsychotic drugs are commonly used by clinicians to treat patients with PDP. The goal of this review was to summarize the challenges of switching antipsychotic drugs in patients with PDP, and to provide consensus guidance on approaches to switching from atypical antipsychotics to pimavanserin. Understanding the receptor binding and safety profile of antipsychotics should guide providers in treating symptoms associated



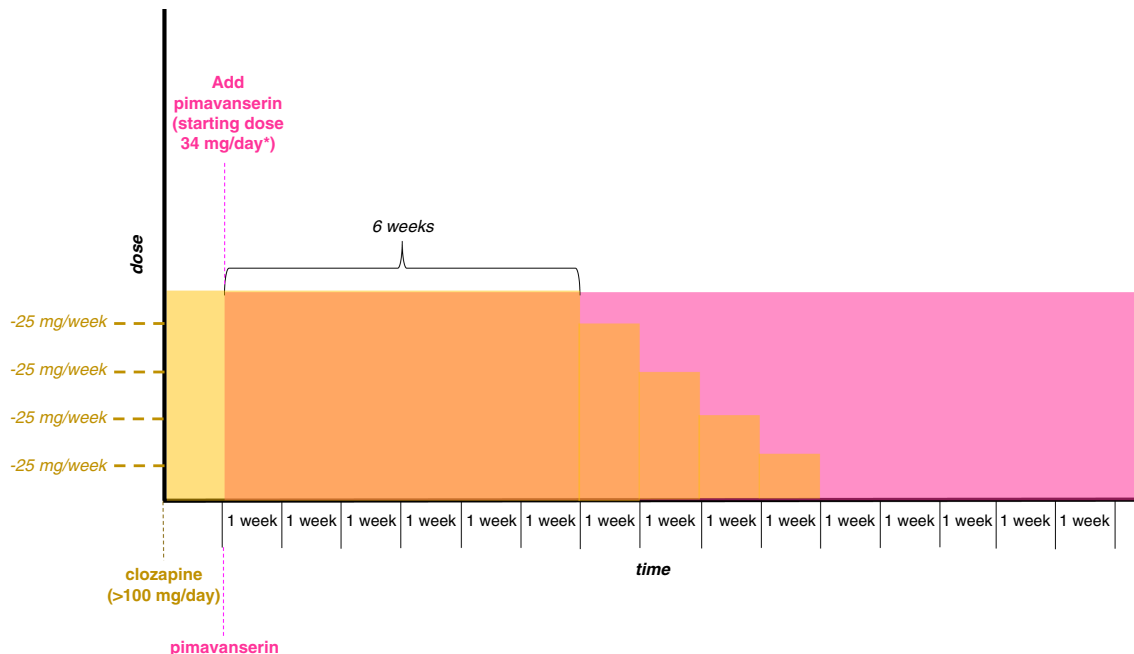


FIGURE 6. Patients currently taking clozapine (>100 mg/day).

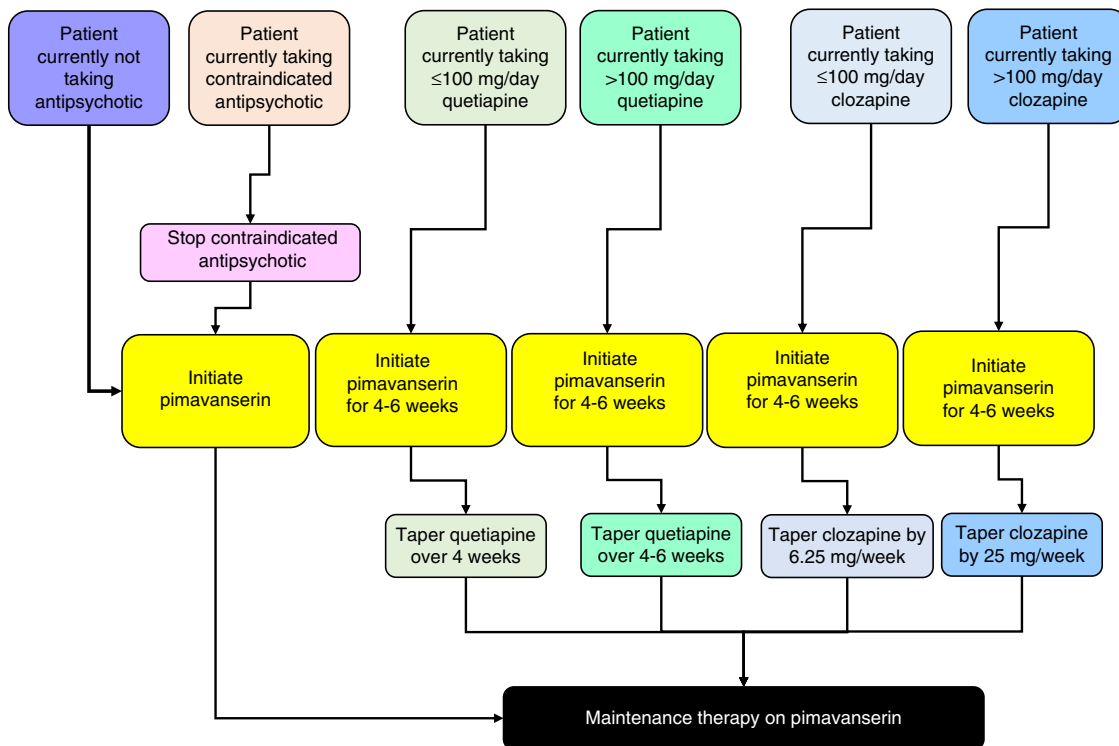


FIGURE 7. Algorithm for initiating pimavanserin.

with PDP. In the absence of controlled clinical trials aimed at evaluating the optimal conditions for switching, a challenge for clinicians is to determine the type of discontinuation (abrupt vs tapered) for the current antipsychotic drug and the timing and starting dose of

the new medication in order to maintain optimal receptor occupancy and limit the risks of rebound effects. Most commonly, according to clinical experience, when switching from quetiapine to pimavanserin, 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. The overall algorithm suggested as guidance for switching to pimavanserin for PDP patients taking an antipsychotic is summarized in Figure 7. Ultimately, the optimal methods for switching will depend not only on the pharmacology and safety of antipsychotic drugs, but also on individual patient profiles (ie, a precision medicine approach).

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