UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

Palliative Care Pharmacy PHAST PHACT

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TODAY'S TOPIC:

What's New in Palliative Care Medications (2017)

Drug #3: Pimavanserin (Nuplazid®)

Background:

Pimavanserin is an antitypical antipsychotic:

- Initial US approval: 2016
- The first and only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP)
- Available as 17mg tablets only

Importance:

Psychosis occurs in almost 50% of patients suffering with Parkinson's disease. This can create a clinical conundrum - as traditional agents, can exacerbate other Parkinson's disease related symptoms. Guidelines support the use of second-generation antipsychotics (SGAs) as they are less likely to cause extrapyramidal symptoms (ie, quetiapine, clozapine) and suggest using clozapine as initial therapy because it has the strongest evidence. However, clozapine's use is limited by many nonmotor adverse effects (eg, orthostasis, sialorrhea) and REMS monitoring for severe neutropenia. Pimavanserin was granted breakthrough therapy status and a priority review, given there is no approved medication for PDP. As Parkinson's disease can be a common diagnosis managed by palliative care providers, they should be aware of this innovative agent.

Palliative Care Pharmacy Team:

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

Pharmacology:

MoA	Exact mechanism is unknown – but could help with PDP through a combination of inverse agonist and antagonist activity at serotonin 5-H_{T2}A receptors and to a lesser extent at serotonin 5-HT_2C receptors
ADME:	A: Tmax: 6 hours, not affected by food D: highly protein bound M: mediated by CYP3A4 and CYP2D6; one major metabolite: AC-279 (active) E: T ½: 57 hours (200 hours for AC-279). Only 1-2% of active compound and metabolite found in the urine and feces
DI:	• Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce dose by one-half • Strong CYP3A4 Inducers: Monitor for reduced efficacy. Increase in dosage may be needed

Key: MoA: Mechanism of Action; ADME: Absorption, Distribution, Metabolism, and Excretion; DI: Drug Interactions; Tmax: time until max concentration; T ½: terminal half-life; Cmax: max concentration; AUC: area under the curve

Other Clinical Points:

Contraindications:	- Hypersensitivity
Warnings and Precautions:	- QTc prolongation
Dosing:	34mg PO once daily (2, 17mg tablets) - Not recommended in patients with severe renal impairment (CrCl <30 mL/min) - Has not been evaluated in patients with severe hepatic impairment
ADRs:	- Most common: Peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%)

Key: ADRs: adverse drug reactions

The Literature:

Pimavanserin was brought to the market through phase II and phase III trials. Below is the phase II trial, which was not as positive as you may hope…

- Neuropsychopharmacology. 2010 Mar;35(4):881-92.
  Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis (PDP).
  - Objective: To compare the tolerability and efficacy of pimavanserin versus placebo in 60 patients suffering with L-DOPA or dopamine (DA) agonist-induced PDP

- Methods: Double-blind, randomized multicenter 28-day study. Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III. Antipsychotic efficacy was evaluated using multiple measures from the Scale for the Assessment of Positive Symptoms (SAPS) and a UPDRS Part I psychosis-relevant item
- Results: Pimavanserin-treated patients showed significantly greater improvement in some but not all measures of psychosis, including SAPS global measures of hallucinations and delusions, persecutory delusions, and the UPDRS measure of delusions and hallucinations. Pimavanserin did not differentiate from placebo with regards to motor impairment, sedation, hypotension, or other side effects
- Conclusion: "… These results support the hypothesis that attenuation of psychosis secondary to DA receptor stimulation in PDP may be achieved through selective 5-HT(2A) receptor antagonism."
- *Discussion:* Remember most individual parameters trended toward improvement with pimavanserin but were not statistically significant. Further studies further support its use however

So… What does this all mean Jenn?

- As above, this is the first and only FDA approved agent for Parkinson's disease psychosis. The dopamine-sparing effects of pimavanserin offer an option that may help improve PDP without worsening motor function
- Although the results of 1 phase II trial and 2 phase III trials were not statistically significant, pimavanserin met criteria for breakthrough status by demonstrating efficacy on a clinically significant end point in a single phase III trial, that was used to support its FDA approval
- Its efficacy is arguably slim. The primary outcome in the phase III trial (a difference in 3 points on the SAPS-PD) is tough because the SAPS-PD is 45-points. Below is that scale:

Scale for the Assessment of Positive Symptoms, Parkinson's Disease-Adapted (SAPS-PD)	Efficacy	• Hallucinations (5) • Delusions (4)	Each item rated from score of "0" (absent) to "5" (severe)	0 to 45	Assesses only those items of the hallucinations and delusions domains of SAPS that occur frequently in and are sensitive to PDP

- In regards to ADRs: the risk for orthostasis with pimavanserin is lower than with quetiapine or clozapine. Although pimavanserin is associated with dose-dependent QTc prolongation (7 msec), it may prolong the QTc less than reported with quetiapine (14.5 ± 12.7 msec)
- Pimavanserin for PDP is promising; however, its use may be limited by cost, insurance coverage, and availability only through select specialty pharmacies; therefore; unlikely you will see within UPMC because of cost
- Quetiapine will likely remain the initial therapy for PDP

Geriatric Considerations:

- No dose-related considerations
- As still an antipsychotic, be thoughtful of BBW and other considerations

Stay tuned for future PCP Phast Phacts on pimavanserin.

CLINICAL PEARL:
Pimavanserin is an atypical antipsychotic brought to the market in 2016 as the first agent FDA approved for the management of Parkinson's disease psychosis.