

Management of Psychosis in Parkinson's Disease

A Case Study

Pharmscript

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Participants will be able to:

1. Assess hallucinations, delusions and illusions specific to Parkinson's disease
2. Understand the evidence-based research on morbidity and mortality when quetiapine is prescribed for Parkinson's psychosis
3. Correlate side effects of dopaminergic antipsychotics to QM's (*falls, movement, ADL, anti-anxiety, hypnotics*)

Participants will be able to:

4. Learn how pimavanserin can decrease risk for F-tags 757 and 758 and other adverse outcomes.
5. Describe advantages of using a non-dopaminergic antipsychotic with no negative impact on motor function in Parkinson's psychosis

Case Study of PDP

Fictitious name: Mr. Steve Miller

75 yo WSM with Parkinson's
Psych Hx: MDD, Anxiety
PCP ordered Dementia Consult
Agitation and weekly falls
Geri-chair w helmet/1:1 care.



Medical/Geropsychiatric History:

- **Pmh:** PD, dysphagia, triple bypass surgery (CV risk)
- **Past psych Hx:** Anxiety, depression, hospitalization for psychotic depression when living in Florida
- **Current Dx of schizophrenia on NH chart**
 - Past record review: Son denied schizophrenia Dx
 - Importance of reviewing medical records
- **Haldol** ordered by a psychiatrist! Sent him all articles I cover in these slides and was main incentive for publishing 2 articles on dementia

1st 3 meds from both current/prior med list cause falls!!

Current Psych Meds

- Haloperidol 2 mg bid
- Clonazepam 1 mg HS
- Trazadone 50 mg HS

Previous Psych Meds

- Risperidone 0.25 mg qd
- Xanax 1 mg HS
- Depakote 250 bid
- Sertraline 25 mg daily
- Trazadone 100 mg daily

Mr. Miller's 3 Hospitalizations in 5 months

1. Sept. 2016: Mild subarachnoid hemorrhage: NH fall.
2. July 2016: Geropsych Hospitalization: suicidal due to visual hallucinations: combative and unmanageable.
3. May 2016: s/p fracture of left ileum and pubic ramus

<http://www.beckershospitalreview.com>
2016 average daily cost in Massachusetts

- Subarachnoid hemorrhage: 6 days=\$14,022
- Geropsych admission: 10 days= \$23,370
- Pelvic FX: 4 days: \$9,348



Price of Mr. Miller on wrong meds for PDP

\$46,740 extra \$\$

spent in 5 months during
3 hospitalizations!!



How prevalent are PD Psychotic Symptoms?

- Parkinson's disease psychotic symptoms of presence hallucinations and illusions affect up to 72% with Parkinson's disease
- Visual hallucination prevalence reaches approximately 50% over patients' lifetime



Fénelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. J Neurol Sci. 2010;289(1-2):12-17.

Diagnostic Criteria for Parkinson's Disease Psychosis (PDP)

Presence of at least one of four symptoms:

- Illusions (misinterpretation of visual stimuli)
- False sense of presence
- Hallucinations
- Delusions
- Must already meet the criteria for Parkinson's disease + have recurrent or continuous psychotic symptoms for one month.



PDP Hallucinations

- Hallucinations are typically visual, vivid, and well formed, usually of people or animals.
- Similar patterns consecutively over time
- Occur during sun-downing!



Minor Hallucinatory Signs

- Presence hallucinations:
Someone lurking in corner of room or behind person (spy, imposter)
- Passage hallucinations:
fleeting, vague images



Illusions and Auditory Hallucinations

Illusions: **misperceptions of real visual stimuli**

Auditory hallucinations: less common than visual

- **People talking or whispering**
- **Music playing from another area**
- **Threatening voices**



Delusional content in PDP

Some develop delusions with disease progression.

Major Themes:

- Paranoia
- Spousal infidelity
- Abandonment
- Harm
- Persons with PDP are very fixed in believing their own delusions.



Mr. Miller's Hallucination Types

- Presence Hallucinations:

His 1:1 nursing assistant says he reaches out for things in the air despite the position he is in (supine, sitting)

- Passage Hallucination:

Conversing with Mr. Miller, his head turned to the right following “something” that was not there

Mr. Miller's Persecutory Delusions

- His 1:1 CNA, whom he has a wonderful relationship with: is “trying to kill him.”
- Gets angry at all staff: "I don't like you.”
- Fluctuant nature of his psychosis
 - CNA says they often have normal conversations about the content of movies.
 - Makes appropriate jokes with her.

Assess and Document

Frequency, Severity, Timing & Behaviors of PDP symptoms

- Mr. Miller's average:
 - Day shift: 3-4 X/week, combative
 - Night shift: 5X/week



Objective Assessment

- Appearance: Blank, fixed gaze, mild right tremor, no tardive dyskinesia.
- Mood: Pleasant, receptive to discussing his health
- Speech: Very soft, inarticulate speech
- Thought form: Aware of content of my questions. Giving appropriate answers
- Thought Content: When I told him his psychiatric symptoms were likely due to his Parkinson's, he gave a huge smile and started to clap!
- Attention: Alert, no sign of delirium
- Perception: Aware, with good focus/concentration



How many of you would treat Mr. Miller with an antipsychotic for

- Paranoid delusions? or
- Passage and presence hallucinations? or
- Outbursts 8 times/week?
 - Ask yourself: Yes or No?
 - If so, what medication would you use?

Clozaril/Clozapine or Quetiapine/Seroquel?

- “Clozapine is effective, but is associated with a poor side-effect profile and the necessity for frequent blood draws.
- Clinicians prefer quetiapine for its theoretically better safety profile, although there is no evidence for efficacy in treating psychosis.
- All atypical antipsychotics are associated with increased mortality in this patient population...”



Antipsychotic risk in Parkinson's disease with stable physical health: 10 yr. VA data

180-day mortality rate on two groups of 7877 veterans:

- 1st group started antipsychotic (AP) Rx for PD
- 2nd group did not start antipsychotic RX

Parkinson's patients taking antipsychotics were associated with greater than twice the risk of death compared with those who did not take antipsychotics.

How MUCH risk for different antipsychotics?

Same Study:

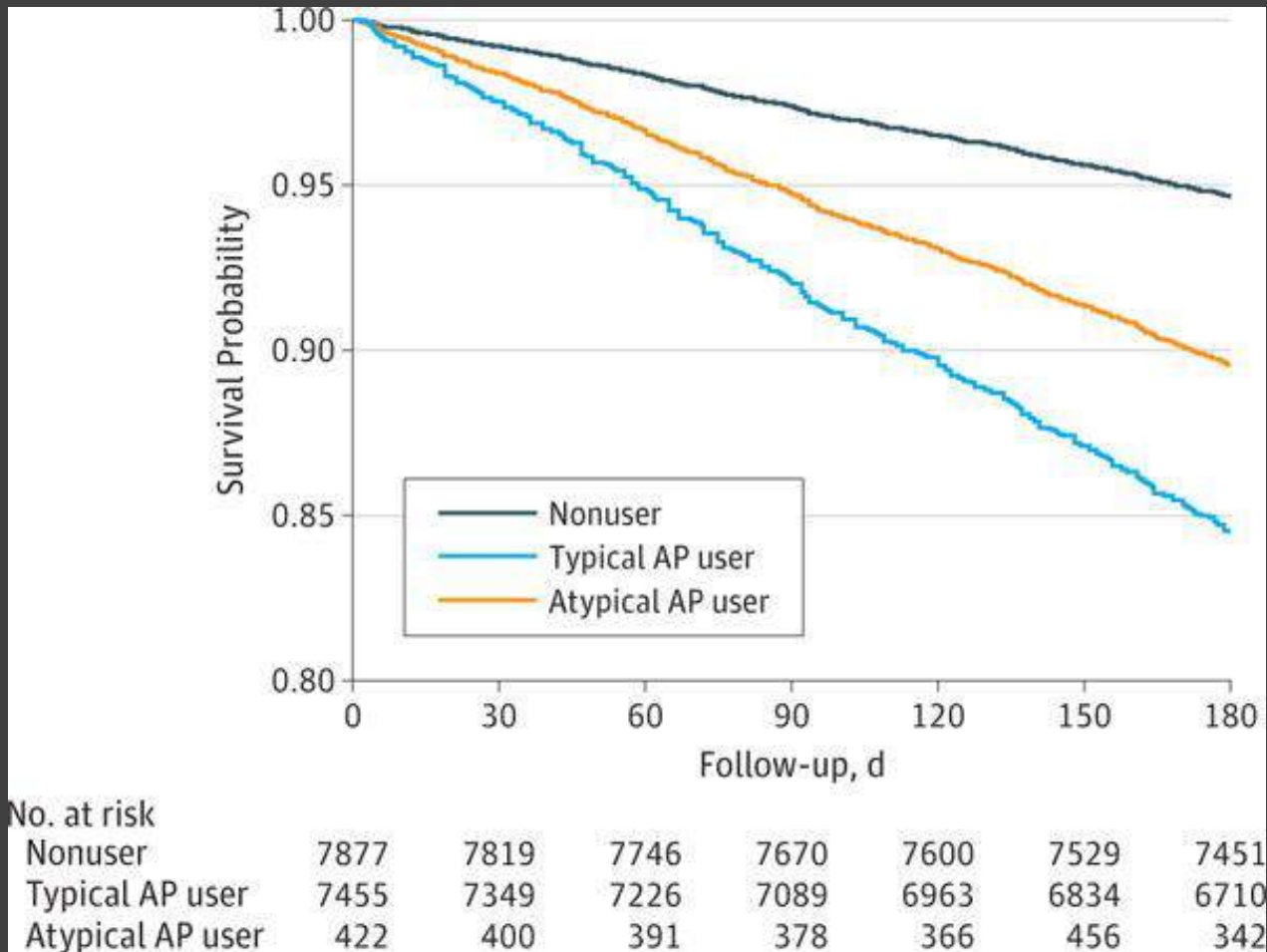
Antipsychotic mortality risk in idiopathic PD with stable physical health.

Hazard ratio: More than double the risk for each:

- Olanzapine: 2.79
- Risperidone: 2.46
- Quetiapine: 2.16



180-day survival on antipsychotics



Weintraub D et al. JAMA Neuro. 2016 May

1;73(5):535-41.



Antipsychotic Use and Physical Morbidity in Parkinson's disease.

- Weintraub's same study also evaluated morbidity/physical illness
 - 6,679 PD pairs studied
 - Any antipsychotic use was associated w an increased risk
 - ED visit (HR 1.64)
 - Inpatient care (HR 1.58)
 - OP visits (HR 1.08)
 - Risk was significantly higher for atypical antipsychotics vs non-use for ER, hospital admission, outpatient visits



Quetiapine for Psychosis in PD and Neurodegenerative Parkinson's disorders

- Systematic review of multiple randomized trials with high-level evidence regarding the role of quetiapine in the treatment of psychosis in patients with diagnoses of Parkinson disease, Lewy body dementia, or any other neurodegenerative parkinsonism.

Quetiapine for Psychosis in PD and Neurodegenerative Parkinson's disorders

- 7 studies w 241 pts met criteria
- Quetiapine failed to significantly reduce psychotic symptoms compared to placebo when objectively assessed using Brief Psychotic Rating Scale

What are the symptoms on the **Brief Psychotic Rating Scale** Quetiapine failed to reduce?

- Somatic preoccupations
- Anxiety
- Depression
- Suicidality
- Guilt
- Hostility
- Euphoria
- Grandiosity
- Suspiciousness
- Hallucinations
- Unusual thought content
- Bizarre behavior
- Disorientation
- Disorganized speech
- Blunted affect
- Emotional withdrawal

[https://www.public-](https://www.public-health.uiowa.edu/icmha/outreach/documents/BPRS_expanded.PDF)

[health.uiowa.edu/icmha/outreach/documents/BPRS_expanded.PDF](https://www.public-health.uiowa.edu/icmha/outreach/documents/BPRS_expanded.PDF)



All dopaminergic (D2) antipsychotics (atypical and typical) are **not** safe or proven effective for PDP or other dementias

Dopaminergic (D2) antipsychotics cause falls in elders
Falls and fractures are a much higher risk in Parkinson's
PD pts already have gait abnormalities and orthostatic autonomic dysfunction!

Are there other options that we have?

Is there something that does not target the D2 receptor?

Is ANY antipsychotic FDA approved for Parkinson's psychosis?

Do surveyors understand the difference between D2 and non D2 antipsychotics?



Pimavanserin/Nuplazid targets only
5HT_{2A} receptor (lesser 5 HT_{2c})

SSIA: Selective Serotonin Inverse Agonist

“...the serotonin 5-HT_{2A} receptor inverse agonist pimavanserin (*Nuplazid*) was recently approved by the US FDA for the treatment of PDP and may prove to be a more targeted therapy without the downsides of atypical antipsychotics.”

Does not touch other 20+ serotonin receptors!



New 5HT2A selective antipsychotic, Pimavanserin (Nuplazid)

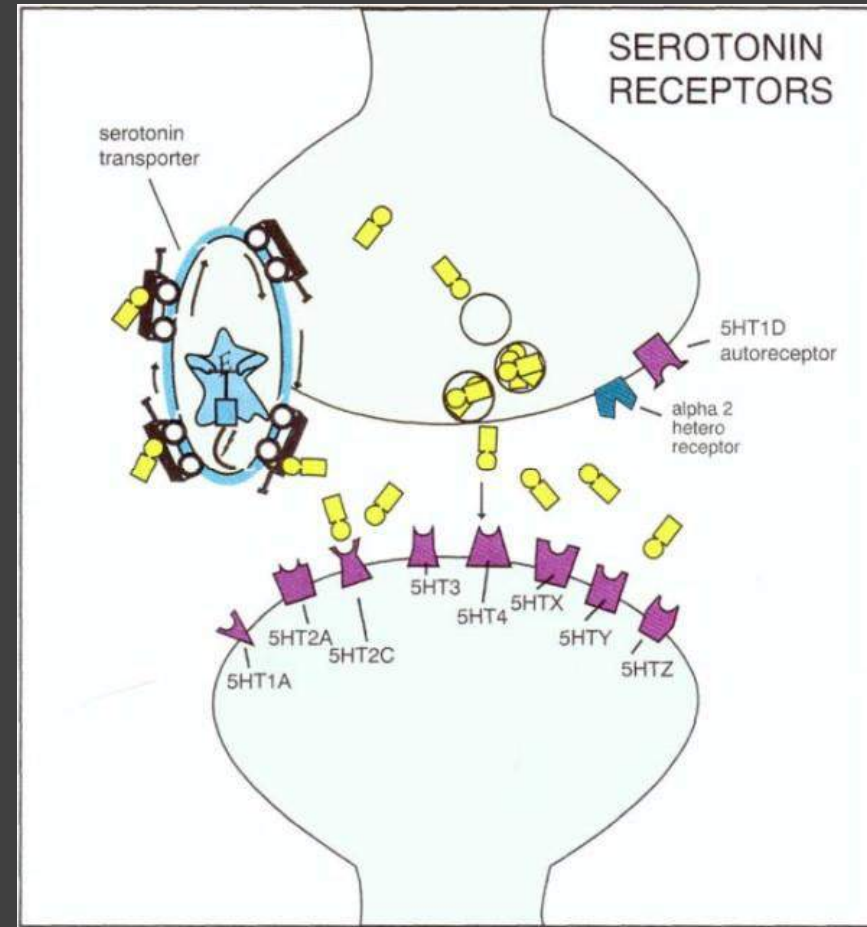
Does not affect Dopamine D2 receptor

- Accelerated FDA approval: released in 2016 for PDP:
Selective Serotonin Inverse Agonist:
- Fully turns off the **5HT2A receptor**: even basal activity
- NUPLAZID® **is indicated** for the treatment of hallucinations and delusions associated with Parkinson's disease **psychosis**



The 5HT-2A receptor and Parkinson's Hallucinations

- Individuals with PDP visual hallucinations have increased serotonin 5 HT- 2A receptor binding in the brain's ventral visual pathway.
- Abnormality in the structure and function of the 5-HT_{2A} receptor is associated with hallucinogenic drugs (LSD)



2017 article: Dopaminergic Antipsychotics (*D2 receptor*) effects on gait, morbidity, meds

- (D2)Antipsychotic use in PD was associated with
 - Unsteady gait
 - Higher comorbidity
 - Greater number of medications
 - Psychosis and aggression
 - Greater cognitive & functional impairment
 - Urinary incontinence.



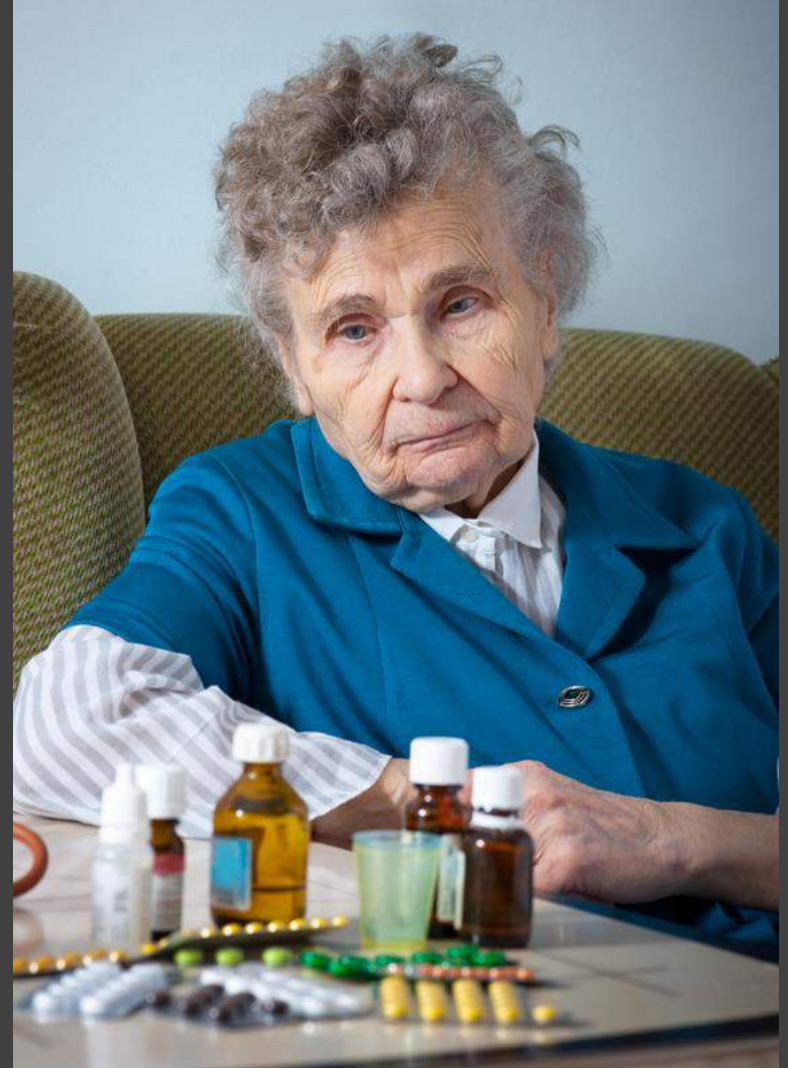
Scanland S, Bielinski T.

<http://www.todaysgeriatricmedicine.com/archive/MJ17p18.shtml>

- Pimavanserin (Nuplazid) 1st in a new class of medications offering treatment for the hallucinations and delusions of PDP
- Unlike all previous antipsychotics, it has no D2 activity. It has "**zero**" **dopaminergic, adrenergic, histaminergic, or muscarinic** receptor affinity.



What do Dopamine-
receptor
antipsychotics cause
in side effects?



Black Box warning 2017 update for Falls in Antipsychotics

“Antipsychotic drugs can cause somnolence, postural hypotension, and motor and sensory instability that could lead to falls and subsequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, **fall risk assessments** should be done when initiating treatment with an antipsychotic and should be repeated in patients on long-term therapy.”



Does Pimavanserin/Nuplazid really work?

- Trial results of pimavanserin:
- Clinically significant reduction of hallucinations and delusions in six weeks
- **(37% reduction in the treatment group vs 14% placebo)** in patients who had PDP symptoms for several years.



Cummings J, Isaacson S, Mills R, et al.
Pimavanserin for patients with Parkinson's
disease psychosis: a randomized, placebo-
controlled phase 3 trial. *Lancet*.
2014;383(9916):533-540.

Will Pimavanserin/Nuplazid affect motor function in PD?

- Unlike previous atypical and typical antipsychotics with dopaminergic activity, there was **no treatment-related worsening of the subjects' motor symptoms.**
- **Unified Parkinson's Disease Rating Scale:** Measures all motor symptoms in Parkinson's disease! **NO worsening of:**
- **Falling, ability to walk, dress, arise from chair, gait freeze, rigidity, salivation, dysphagia, utensil use.**

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2014;383(9916):533-540.



Pimavanserin (Nuplazid) advantage over all other dopamine binding antipsychotics

- Pimavanserin (Nuplazid) has NO negative affect on gait, fall risk or motor function as it only targets the one serotonin receptor and does not touch dopamine receptors

Assessment of Mr. Miller and medication risks

- Parkinson's Disease Psychosis with persecutory delusions and illusions
- Very high fall risk and autonomic instability of Parkinson's disease
 - (Haloperidol: highest extrapyramidal side effects of all antipsychotics)

PLAN: Cross Titration from Haldol to Pimavanserin/Nuplazid

- Decrease Haloperidol/Haldol to 2 mg in AM and 1 mg HS
- 5 days later start Pimavanserin/Nuplazid 34 mg (two tabs daily: comes only in 17 mg)
- 5 days after Pimavanserin/Nuplazid started decrease Haldol to 1 mg bid for 5 days
- Then decrease Haldol to 1 mg daily for 5 days and then d/c.

PLAN

- Mr. Miller's a very high fall risk with dopamine deficiency and autonomic instability of Parkinson's disease
 - (Pt had two previous hospitalizations for fractures and subarachnoid hemorrhage)

4 months later

Was symptom free of hallucinations and delusions from January through April.

Excellent response to Pimavanserin (Nuplazid)

F757: Drug Regimen is Free From Unnecessary Drugs.

F758: Free from Unnecessary Psychotropic Meds/PRN

Pimavanserin/Nuplazid 34 mg daily

Mr. Miller is accepting staff assistance for activity participation, likes watching TV, going outside, social and discussion groups, enjoys musical entertainment, visiting w family when they come in. Eats meals in day room with other residents, watching movies and discussion of 1:1 activity visits. No additional falls!



Quality Measures: Improved by optimal PDP Rx

1. Ability to move independently worsened
2. % whose ADL needs increased
3. % on antianxiety or hypnotic
4. % on antipsychotic
5. 1 or more falls with major injury

Questions to Ask Yourself Lessons Learned from Mr. Miller

If you continue Quetiapine, Risperidone, Olanzapine, Haloperidol, are you willing to:

- Spend more time feeding patients (dysphagia, problem with utensils)?
- Inform Parkinson's residents/families verbally and sign consent that their D2 antipsychotic will:
 - Double the risk of their death?
 - Will have more trips to the ER and hospital?
 - Their cognition and function will decline? (staff hours up)
 - Increase urinary incontinence (and staff time to change)

Need Help Steering your Ship (Facility/Providers? in the Right Direction?

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Virtual/Live **SOS** for prescribers/QMs/resident outcomes/
staff hours due to behaviors



Differentiating Dementias. Two-part manuscript series on Alzheimer's and other dementias

- Today's Geriatric Medicine (online):
- FREE: Please share to prevent problems that you'll see Mr. Miller had:
- Susan Scanland/ Tyler Bielinski
- Todaysgeriatricmedicine.com Go to archive page and scroll down
- March/April 2017: The Dementia Workup and Management of Alzheimer's Disease
- May/June 2017: Non-Alzheimer's Dementias (includes Parkinson's dementia/ psychosis)

