PSYCHOSIS IN PARKINSON'S DISEASE
Objectives

• Identify neurobiological substrates associated with Parkinson’s disease psychosis

• Describe the differences between older antipsychotics and novel therapies for Parkinson’s disease psychosis

• Utilize appropriate treatment and switching strategies for management of patients with Parkinson’s disease psychosis
Parkinson’s Disease Psychosis

- Parkinson’s disease (PD) itself is a chronic, progressive, neurodegenerative disease characterized by both motor and non-motor features.

- Parkinson’s disease psychosis (PDP) is a common non-motor neuropsychiatric manifestation of PD; up to 60% of patients with PD experience psychotic symptoms for at least one month at some point during the course of their illness.

- PDP is characterized by hallucinations (often visual), and delusions (typically paranoid, such as spousal infidelity), as well as illusions and a false sense of presence.

- The burden of PDP is substantial for both the patient and the caregiver; PDP is a common reason for hospital admission, nursing home placement, and increased mortality.

Clinical Symptoms and Time Course of Parkinson’s Disease

Degree of Disability

Pre-motor/prodromal period

Parkinson’s disease diagnosis

Early

Advanced/late

Fluctuations
Dyskinesia

Bradykinesia
Rigidity
Tremor

Urinary symptoms
Orthostatic hypotension
Dementia

Psychosis

Dysphagia
Postural instability
Freezing of gait
Falls

Complications

Motor

Non-motor

Time (years)

Constipation
RBD
EDS
Hyposmia
Depression
Pain
Fatigue
MCI

1. Image adapted from Kalia LV, Lang AE. Lancet. 2015;386:896-812.

EDS: excessive daytime sleepiness; MCI: mild cognitive impairment; RBD: REM Behavior Disorder
Parkinson’s Disease Pathology Is Complex and Progresses Over Time, Affecting Many Areas of the Brain

Stages in the Evolution of PD-related Pathology¹

1. Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone

2. 1 + Lesions in the caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex

3. 2 + Midbrain lesions, in particular in the pars compacta of the substantia nigra

4. 3 + Prosencephalic lesions, cortical involvement confined to the temporal mesocortex and allocortex

5. 4 + Lesions in high order sensory association areas of the neocortex and prefrontal neocortex

6. 5 + Lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

The Parkinson’s Complex²

- Parkinsonism
- Substantia Nigra
- Pons
- Basal forebrain
- Medulla
- Amygdala
- Hypothalamus
- Olfactory bulb
- Spinal cord*
- Peripheral autonomic nervous system**
- Neocortex
- Temporal cortex
- Olfactory cortex

*Intermediolateral column
**Heart, intestinal track, bladder

Parkinson’s Disease Psychosis: A Serotonin-Dopamine Imbalance

Psychosis can result from overaction of the mesolimbic dopamine pathway$^{1-3}$

Hallucinations can result from activation of 5HT2 receptors$^4$

Parkinson’s Disease Psychosis: A Serotonin-Dopamine Imbalance

Psychosis can result from overaction of the mesolimbic dopamine pathway\textsuperscript{1-3}

Hallucinations can result from activation of 5HT2 receptors\textsuperscript{4}

And wait, there’s more... overactivation of downstream \textbf{glutamate} signaling to the Ventral Tegmental Area may result in excess dopamine in the ventral striatum via the mesolimbic pathway

Who Gets Parkinson’s Disease Psychosis (PDP)?

• Usually more advanced PD patients ≥ 10 years from diagnosis
  • Early hallucinators who develop symptoms within 12 months of PD diagnosis have alternate diagnoses (e.g., Lewy body disease (LBD))

• 25%-50%+ lifetime prevalence in community samples

• Strong association with cognitive impairment. In cross-sectional studies, visual hallucinations occur in:
  • 70% of PD patients with dementia
  • 10-20% of PD patients without dementia

• Other clinical associations: sleep disturbances (especially REM behavior disorder), depression, PD motor severity, axial impairment

• No association with L-dopa equivalent daily dosage (LEDD)

Diagnostic Criteria for Parkinson's Disease Psychosis (PDP)

2007 Provisional NINDS-NIMH Diagnostic Criteria for PDP

At least 1 of the following symptoms:

- False Sense of Presence
  - Feeling someone is present

- Illusions
  - Perceived distortion of reality
  - Often visual

- Hallucinations
  - Abnormal perception
  - Usually visual and not upsetting, may be pleasant

- Delusions
  - False or irrational belief not based on reality

May occur with or without:

- Insight
- Dementia
- Parkinson's disease Tx

Symptoms must occur in patients after onset of PD

Symptoms recurrent or continuous for at least 1 month

NINDS: National Institute of Neurological Disorders and Stroke

Other Causes Need to be Excluded

Differential diagnosis
- Delirium
- Schizophrenia
- Alzheimer’s disease psychosis
- Major depression with psychosis
- Other psychiatric disorders

Symptoms of PDP

- Visual hallucinations (VH) with a clear sensorium are the most common psychotic symptom (~90%)
  - VH are typically well-formed images of people or animals; they are rarely images of inanimate objects; content tends to recur

- Auditory hallucinations are less common (8-13%) and rarely occur in isolation

- Delusions are primarily paranoid (e.g., abandonment, infidelity)

Symptom Evolution

Frequency: intermittent; usually several times per day; seconds to minutes in duration

Environment: VH often occur during periods of low ambient stimulation, especially in the evening

Minor hallucinations: anwesenheit and illusions/passage phenomena are quite common (up to 40%)
  
  • Fleeting; nondisruptive; often not reported
  
  • May remit for periods, but eventually evolve into VH

Insight: retained initially, but gradually lost as severity increases or delusions develop

PDP Treatment (Pre-1990)

• DA agonist dose reduction
  • May be poorly tolerated; significant on/off and freezing issues

• Remove centrally acting anticholinergics (e.g., oxybutynin, tolterodine [Detrol], solifenacin [Vesicare])

• Typical antipsychotics
  • Usually poorly tolerated; significant risk of motoric worsening

Double-Blind Atypical Antipsychotic Trials for the Treatment of PDP

<table>
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<th>Drug</th>
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<th>Effects on Motor Function</th>
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<td>+ *</td>
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* Improved motor function

The Clozapine Problem

• Outstanding efficacy, at doses 3–5% of those used for schizophrenia (6.25–50 mg/day)

• Weekly ANC monitoring for agranulocytosis for 6 months (then biweekly for 6 months, then monthly at ≥ 12 months)

• Significant sedation (H1 and M1), orthostasis (\(\alpha_1\))
Pimavanserin (PIM)

• PIM is a highly selective serotonin 5-HT2A receptor inverse agonist/antagonist

• Approved in the US in April 2016 for the treatment of hallucinations and delusions associated with PDP

• Because PIM has no measurable activity at dopaminergic, histaminergic, adrenergic, or muscarinic receptors, this would predict a favorable tolerability profile in that motor symptoms would not be expected to worsen, and urinary retention, constipation, sedation, weight gain, akathisia, and postural hypotension would not be expected obstacles to using PIM

• The recommended dose is 34 mg taken once daily, any time of day, with or without food; titration is not necessary; be mindful when switching!

Pimavanserin: A Selective 5HT2A Inverse Agonist for the Treatment of PDP

The Pivotal Trial

- 6-week, randomized, double-blind, placebo-controlled study
- Antipsychotics not permitted, but ongoing antiparkinsonian medication or deep brain stimulation (DBS) was allowed
- 2-week nonpharmacological lead-in to limit placebo response
- Random allocation to pimavanserin 40 mg/d (n=95) or placebo (n=90)

- Primary outcome: Parkinson's disease-adapted scale for assessment of positive symptoms (SAPS-PD) as assessed by central, independent raters
  - Secondary measures included Unified Parkinson's Disease Rating Scales II (ADL) and III (motor exam), SAPS-H (hallucinations), and SAPS-D (delusions)

Pimavanserin Kinetic and Metabolism

- **Pharmacokinetics**
  - Half-life \(t_{1/2}\) is 57 hours
  - \(t_{1/2}\) of active, N-demethylated metabolite is 200 hours
  - \(T_{\text{max}}\) of 6 hours (range 4-24)

- **Metabolism**
  - CYP3A4 is the major enzyme responsible for pimavanserin metabolism
    - Recommend 50% dose reduction when used with strong 3A4 inhibitors

- **Dosing**
  - 34 mg/day taken once daily; no titration required
Concepts Related To Benefit / Risk: 
Effect Size - Number Needed To Treat

• NNT is one measure of effect size

• It is independent of $p$-value and does not say anything about the likelihood of the difference between treatments being due to chance alone

• Helps you judge the clinical significance of a statistically significant result

Number Needed To Treat

• How many patients would you need to treat with Drug A instead of Drug B before you would encounter one extra outcome of interest, such as response

The smaller the NNT, the larger the differences between the two drugs

What Is NNH?

• NNH is Number Needed to Harm

• We would use NNH when referring to an outcome we are trying to avoid, or to refer to a disadvantage for Drug A versus Drug B

• In calculating NNT, if it is a negative number, we can call it a NNH
What Is A Clinically Important NNT?

• A large NNT of 100 or more means that there is little difference between choosing Drug A or Drug B for the outcome measured

• A small NNT of 2 would be a hugely important difference

• NNT values <10 denote a potentially useful intervention

• NNH values >10 denote a potentially tolerable intervention

• Some NNTs may be clinically important, even if they are relatively large, for example when the outcome is death
Examples of NNT: NNT vs. placebo (and 95% CI) for response* in persons with acute schizophrenia in short-term trials

* Response defined as a ≥30% decrease in the Positive and Negative Syndrome Scale total score or a Clinical Global Impressions-Improvement score of 1 (very much improved) or 2 (much improved); for aripiprazole vs. placebo responder rates were 38% vs. 24%, and for brexpiprazole vs. placebo, 46% vs. 31%
Response Rates for Pimavanserin (PIM) 34 mg vs. Placebo (PBO)

- ≥30% Decrease from Baseline on SAPS-PD: 51.6% (PIM) vs. 35.6% (PBO), NNT 7 (4-52)
- ≥50% Decrease from Baseline on SAPS-PD: 38.9% (PIM) vs. 27.8% (PBO), NNT 9 (ns)
- Score of 1 (very much improved) or 2 (much improved) on the CGI-I: 45.3% (PIM) vs. 24.4% (PBO), NNT 5 (3-14)
- ≥30% Decrease from Baseline on the SAPS-PD or a score of 1 (very much improved) or 2 (much improved) on the CGI-I: 61.1% (PIM) vs. 42.2% (PBO), NNT 6 (3-22)
Response Rates for Pimavanserin (PIM) 34 mg vs. Placebo (PBO)

- **NNT values for response are 5 to 9, depending on definition**

- **≥30% Decrease from Baseline on SAPS-PD**
  - PIM 34 mg: 51.6%
  - PBO: 35.6%

- **≥50% Decrease from Baseline on SAPS-PD**
  - PIM 34 mg: 38.9%
  - PBO: 27.8%

- **Score of 1 (very much improved) or 2 (much improved) on the CGI-I**
  - PIM 34 mg: 45.3%
  - PBO: 24.4%

- **≥30% Decrease from Baseline on the SAPS-PD or a score of 1 (very much improved) or 2 (much improved) on the CGI-I**
  - PIM 34 mg: 61.1%
  - PBO: 42.2%
Robust Response/Remission Rates for PIM 34 mg vs PBO

- Score of 1 (very much improved on CGI-I)
  - PIM 34 mg: 20.0%
  - PBO: 6.7%
  - NNT 8 (5-27)

- 100% Decrease from Baseline on SAPS-PD
  - PIM 34 mg: 13.7%
  - PBO: 1.1%
  - NNT 8 (5-19)
Robust Response/Remission Rates for PIM 34 mg vs PBO

- **Score of 1 (very much improved on CGI-I)**
  - PIM 34 mg: 20.0%
  - PBO: 6.7%
  - **NNT = 8**

- **100% Decrease from Baseline on SAPS-PD**
  - PIM 34 mg: 13.7%
  - PBO: 1.1%
  - **NNT = 8 (5-19)**
Tolerability Outcomes: Summary

• The tolerability pattern of PIM is different from that of second-generation antipsychotics

• NNH values regarding tolerability outcomes were consistently ≥10, and for the most part not statistically significant, or at times showing an advantage for PIM (such as orthostatic hypotension with a NNH of -12)

• Of note, NNH values for PIM (all doses) vs. placebo for somnolence was 138 and for weight gain ≥7% from baseline, -594

• Akathisia was not observed

• There were no observed deleterious effects on mood

Likelihood to be Helped or Harmed (LHH)

- LHH = NNH/NNT and answers the question of how often would one encounter a benefit vs. a harm.

- A useful definition of response is a ≥3 point decrease from baseline on SAPS-PD (a 2.33 point change on the SAPS-PD corresponds to a clinically meaningful 1-unit change in the CGI-I scale).

- The NNT is 4 for a ≥3 point decrease from baseline on SAPS-PD for PIM 34 mg/d vs. placebo and NNH is 21 for the overall tolerability metric of discontinuation because of adverse event from all pooled data for PIM 34 mg/d vs. placebo.

- The resulting LHH is 21/4 = 5.25.
Likelihood to be Helped or Harmed (LHH) II

\[ LHH = 5.25 \]

- Number needed to treat for a 3-point decrease from baseline on SAPS-PD: 4
- Number needed to harm for discontinuation because of an adverse event: 21

PIM 34 mg/d is about 5 times more likely to result in response (≥3 point decrease from baseline on SAPS-PD) than discontinuation because of an adverse event.

LHH = 5.25

Number needed to treat for 3 point decrease from baseline on SAPS-PD
Number needed to harm for discontinuation because of an adverse event

Limitations

• The data analyzed in this study are limited to dichotomous outcomes

• The results may not be generalizable to patients outside the confines of a clinical trial

• Reasons for clinical trial discontinuation can be complex, so that the NNH for discontinuation due to adverse effects in the study may not always generalize to overall tolerability in clinical practice

• The brief (4-6 week) durations of the available controlled studies of PIM limit the sensitivity of calculating NNH for delayed adverse outcomes, and the relatively small sample sizes of the studies limit sensitivity of calculating NNH for uncommon adverse outcomes and sub-population effects

Summary

Psychosis is a common finding in late stage PD and is a major contributor to nursing home placement

- Upregulation/supersensitivity of 5HT2A is the underlying pathophysiological mechanism. Limited association with PD treatment modality.
- Clozapine at very low doses has demonstrated efficacy for PDP but is burdensome and rarely used. Other antipsychotics cause intolerable motoric worsening or are generally ineffective (quetiapine).

Pimavanserin, a potent selective 5HT2A inverse agonist is the only approved agent for PDP

- The absence of D2 antagonism, or affinity for muscarinic, histamine H1, and alpha adrenergic receptors significantly improves tolerability compared to traditional antipsychotics.