Parkinson’s Disease Psychosis: What Mental Health Professionals Need to Know

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Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label use of clozapine, quetiapine, and cholinesterase inhibitors for the treatment of Parkinson’s disease psychosis will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
• This activity has been independently reviewed for balance.
Parkinson’s Disease: A Chronic, Progressive Neurodegenerative Disorder

- Afflicts ~1.0 to 1.5 million people in North America
- Usual onset between 40 and 70 years; peak age of onset at 6th decade
- Affects up to 0.3% of the general population but 1% to 3% of those > 65 years
- Slight male predominance (3:2)
- 40,000 to 60,000 new cases/year
- Prevalence increasing as the population ages – Prevalence 160/100,000

Parkinson’s Disease: A Chronic, Progressive Neurodegenerative Disorder (cont’d)

- Causation
  - Genetic 5% to 10% of cases monogenic
  - 90% sporadic likely due to polygenic predisposition with significant environmental influences and there is no cure
- Underlying dopamine deficit occurs in the basal ganglia region of the brain
- Non-motor and motor symptoms are progressive and worsen over time

Parkinson’s Disease

• PD is a progressive neurological disorder resulting predominantly from the degeneration of dopamine-producing brain cells (important for control of motor function)

Substantia nigra:
Reduction in number of dopamine-producing neurons

Striatum:
Imbalance in activity of dopaminergic and cholinergic neurons

PD = Parkinson’s disease.
Lewy Body

Courtesy of Kapil D. Sethi, MD.
Braak Staging Hypothesis: Stages 1 and 2

- **Stage 1**: Dorsal motor nucleus of the vagus and olfactory bulb

- **Stage 2**: Lower brainstem, including pons (medullary raphe, magnocellular portion of reticular formation, and locus coeruleus)

Braak Staging Hypothesis: Stages 3 and 4

- **Stage 3**: Amygdala, magnocellular nuclei of the basal forebrain, and pars compacta of substantia nigra

- **Stage 4**: Olfactory telencephalic cortex, temporal mesocortex

Braak Staging Hypothesis: Stages 5 and 6

- **Stage 5**: Sensory association areas, prefrontal fields of neocortex

- **Stage 6**: Primary fields of neocortex

Unified Staging System for Lewy Body Disorders (USSLB)

- USSLB 4 Stages
  - **Stage 1**: Olfactory only
  - **Stage 2A**: Brainstem
  - **Stage 2B**: Limbic System
  - **Stage 3**: Brainstem and Limbic System
  - **Stage 4**: Neocortical

- Includes Lewy Body and α-synuclein pathology

Parkinson’s Disease is a Multisystem Disorder

Parkinson’s Disease: Both Motor and Non-Motor

Motor Symptoms
- Cardinal Symptoms
  - Resting tremor
  - Rigidity
  - Bradykinesia
  - Postural instability
- Other Motor Symptoms
  - Festinating gait
  - Micrographia
  - Masked facies
  - Retropulsion
  - Hypophonic speech

Non-Motor Symptoms
- Cognitive Impairment
  - Mild cognitive impairment (MCI), Dementia
- Neuropsychiatric disorders
  - Psychosis
  - Impulse control and related disorders (ICDs)
  - Depression
  - Anxiety
- Autonomic Complications
  - Orthostatic hypotension
  - Constipation
  - Urinary symptoms
  - Sexual dysfunction
- Sleep Disorder
  - Restless legs syndrome (RLS)
  - REM behavior disorder (RBD)
  - Excessive daytime sleepiness (EDS)

Non-motor symptoms may have a greater impact on quality of life, but there are very few treatments approved for them.

Clinical Symptoms and Time Course of PD Progression: Pathological Progression from Prodrome to Advanced Disease

Parkinson’s Disease Psychosis Has a Distinct Clinical Profile: NIMH Diagnostic Criteria

- Primary diagnosis of PD prior to the onset of psychosis
- A diagnosis of PD psychosis requires the presence of 1 of the following symptoms to be recurrent or continuous for at least 1 month in a person with PD:
  - Hallucinations
  - Delusions
  - Illusions
  - False sense of presence
- PD psychosis may occur with or without:
  - Insight
  - Dementia
  - PD treatment

Other potential medical and psychological causes of psychosis must be excluded

Both Intrinsic and Extrinsic Factors Contribute to Parkinson’s Disease Psychosis

Intrinsic Factors
Comorbid Conditions
• Presence of comorbid medical or psychiatric conditions

Evidence for Disease Progression
• PD severity
• PD duration
• Older age
• Cognitive impairment or dementia

Evidence for Neurobiology
• Neurotransmitter abnormalities
• Neural pathways
• Visual processing deficits

Extrinsic Factors
Medications
• Antiparkinson medications (eg, higher levodopa dose, dopamine agonists, amantadine)
• Other medications (eg, anticholinergics)

Environment
• Dim lighting
• Time of day
• Objects in environment

PD Psychosis is a Common But Underrecognized Aspect of PD Likely to Become More Prevalent as Cases of PD Increase

US prevalence of PD is projected to more than double in the next 2 to 3 decades

> 50% of patients with PD will develop PD psychosis during the course of their disease

Patients with PD do not often disclose symptoms of psychosis to their physician

Of the patients that reported each symptom, the percent who did not disclose:

- Hallucinations: 41.5%
- Delusions: 65.2%

Visual Hallucinations are the Most Common Element of PD Psychosis, Generally in Combination with Hallucinations and Delusions in Other Modalities

### SYMPTOMS OF PD PSYCHOSIS

<table>
<thead>
<tr>
<th>Minor Phenomenon</th>
<th>Hallucinations</th>
<th>Delusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presence hallucinations</strong>: The experience that someone is present when no one actually is</td>
<td>Abnormal perceptions without a physical stimulus that can involve any sensory modality and may be simple or complex in form</td>
<td>False, fixed, idiosyncratic beliefs that are maintained despite evidence to the contrary</td>
</tr>
<tr>
<td><strong>Illusions</strong>: Misperceptions of real stimuli that are often visual in nature</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Visual hallucinations** are the most common symptom of PD psychosis; other **auditory, tactile, and olfactory hallucinations** may occur in combination with the visual hallucinations or, more rarely, in isolation.

- Delusions may encompass a variety of themes, including **persecutory** (someone stealing or harming the patient), **jealousy**, and **reference**.

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Benign Hallucinations Do Not Remain Benign

- A study followed 48 PD patients with “benign” hallucinations (UPDRS thought disorder score of 2) who were receiving no treatment for hallucinations for at least 3 years or until a thought disorder score of 3 or 4 occurred.
- 81% progressed to thought disorder scores of 3 or 4.
- 78% of patients who retained a thought disorder score of 2 had their PD medications reduced to treat hallucinations.
- Only 4% of patients were stable (ie, stable, untreated benign hallucinations over time).

UPDRS = Unified Parkinson’s Disease Rating Scale.
The Course of Parkinson’s Disease Psychosis

While insight is retained, patients are often able to cope with symptoms without behavioral disturbances.

Mortality at 3 years is approximately 40% for PD patients with psychosis.

The Burden of Parkinson’s Disease Psychosis

- Caregiver burden increases as PD psychosis symptoms progress
  - > 40% report a decline in physical health
  - 66% report that their close relationships suffer
  - Nearly 50% have scores indicating depression

- Symptoms of psychosis were identified as the reason for 24% of hospital admissions for patients with PD

- PD patients with hallucinations are 2.5 × more likely to be admitted into a nursing home

Pathophysiology of Parkinson’s Disease Psychosis
Patients with PD Lose Serotonergic Neurons and Functioning and, as a Result, May Experience Compensatory Upregulation of 5-HT Receptors

There is clear evidence of serotonergic dysfunction in PD

- Loss of 5-HT neurons in multiple brain pathways
- Reduced SERT binding
- Lewy body pathology in the raphe nuclei (primarily serotonergic neurons)
- Lewy body pathology in the cortex in later disease

Loss of raphe nuclei and certain cortical neurons may result in changes in serotonin function to compensate – particularly upregulation of 5-HT$_{2A}$ receptors in several brain regions

Dysfunction of the serotonergic system is linked to PD psychosis

SERT = serotonin transporter.
Patients with Parkinson’s Disease and Hallucinations Have Increased 5-HT$_{2A}$ Receptor Binding

Patients with PD and hallucinations have increased 5-HT$_{2A}$ receptor binding in several regions of the brain, including the ventral visual pathway.

5-HT$_{2A}$ Receptor Binding Potential

*The red highlighted regions indicate areas with increased 5-HT$_{2A}$ receptor binding compared to patients with PD without hallucinations.

VH = visual hallucination; OFC = orbitofrontal cortex; IOG = inferior occipital gyrus; FG = fusiform gyrus; ITC = inferior temporal cortex; DLPFC = dorsolateral prefrontal cortex; PCC = posterior cingulate cortex; R = right; L = left.

Increased 5-HT$_{2A}$ Receptor Levels on Autopsy in PD Patients with Visual Hallucinations

45.6% increase in the levels of [$^3$H]-ketanserin binding in the inferolateral temporal cortex, a critical structure in visual processing, of PD patients with VH compared to PD patients without VH.

Reduced Raphe SERT Availability and Parkinson’s Disease Symptoms

• Reduced raphe SERT availability is associated with the severity of resting tremor but not non-motor symptoms (fatigue, depression, and sleep disturbance) in *de novo* PD

• Other studies have linked serotonergic dysfunction, and particularly the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor activity, to L-dopa-induced dyskinesias

Serotonin–Dopamine Balance

Dopamine Theory:
Hyperactive in mesolimbic pathway

GABA = gamma-aminobutyric acid.
Parkinson’s Disease: Nigrostriatal Dopamine/D₂ Deficiency

3 Hypotheses of Psychosis

- **Dopamine Theory**: Hyperactive in mesolimbic pathway
- **Serotonin Theory**: $5$-HT$_{2A}$ receptor hyperfunction in the cortex
- **NMDA Theory**: NMDA receptor hypofunction

- Interconnected Pathways with one or more active in any one psychotic patient

NMDA = N-methyl-D-aspartate.
Cocaine and amphetamines stimulate D₂ receptors and cause auditory hallucinations and paranoid delusions with lack of insight.
Serotonin Theory: 5-HT$_{2A}$ Receptor Hyperfunction in the Cortex

- LSD and psilocybin simulate 5-HT$_{2A}$ receptors and visual hallucinations, mystical delusions often with preserved insight
- Haloperidol is unable to block the visual hallucinations, but 5-HT$_{2A}$ antagonists are effective

PCP and ketamine are NMDA receptor antagonists (in addition to amantadine) and cause visual hallucinations and paranoid delusions with lack of insight.

Parkinson’s Disease
Psychosis:
Cortical Serotonin/5-HT$_{2A}$ and Mesolimbic Dopamine/D$_{2}$ Excess Superimposed Upon Nigrostriatal Dopamine/D$_{2}$ Deficiency

L-DOPA Psychosis: Dorsal to Ventral Striatal Shift and Dopamine Overdose

= Lewy body

Treatment of Parkinson’s Disease Psychosis
Treating Psychosis in Parkinson’s Disease

- Identify and address systemic illnesses that may trigger psychosis (eg, infection, delirium, toxic etiologies)
- Consider discontinuing any nonessential non-PD medications that could contribute to psychosis (eg, anticholinergics, tricyclic antidepressants, benzodiazepines, and opioids)

Managing psychosis and its behavioral and emotional consequences through nonpharmacologic methods (eg, coping skills, cognitive-behavioral therapy, psychoeducation) should also be discussed with patient and family.

Carefully Consider the Consequences to the Patient’s Motor Function if Adjusting Dopaminergic Therapies to Address PD Psychosis

- Anticholinergics
- Amantadine
- Monoamine oxidase B inhibitors (eg, rasagiline and selegiline)
- Dopamine agonists (eg, pramipexole)
- Catechol-O-methyltransferase inhibitors (eg, entacapone)
- Adjust levodopa doses

Reduce/ optimize drugs to reduce psychosis (expert opinion regarding order):

Decreasing Dopamine replacement therapy may address psychosis, but generally worsens motor symptoms, presenting a therapeutic bind.

Types of Antipsychotics

**Typical antipsychotics** (eg, haloperidol)
- Share the primary pharmacologic property of D$_2$ receptor antagonism

**Atypical antipsychotics** (eg, clozapine, risperidone, aripiprazole)
- May act via simultaneous 5-HT$_{2A}$ and D$_2$ antagonism, partial agonist actions at 5-HT$_{1A}$ receptors, partial agonist actions at D$_2$ receptors, or a combination of these mechanisms

It is important to recognize that neither typical or atypical antipsychotics are homogenous groups.

### Receptor Type Selected Potential Effects

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Selected Potential Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine activity</td>
<td>Antipsychotic, anti-manic, EPS, tardive dyskinesia, prolactin elevation</td>
</tr>
<tr>
<td>Serotonergic activity</td>
<td>Anxiolytic, antidepressant, increased appetite, and weight gain (?)</td>
</tr>
<tr>
<td>Histaminergic activity</td>
<td>Anxiolytic, sedation, weight gain</td>
</tr>
<tr>
<td>Muscarinic activity</td>
<td>Cognitive blunting, dry mouth, constipation, urinary retention, blurred vision</td>
</tr>
<tr>
<td>Alpha adrenergic</td>
<td>Orthostatic hypotension, drowsiness, dizziness, syncope, antidepressant</td>
</tr>
</tbody>
</table>

*Effects may vary based upon the specific receptor affinities of each antipsychotic and dose of each antipsychotic.
EPS = extrapyramidal side effects.
Atypical Antipsychotic Groupings by Relative $5$-$HT_2A$ and $D_2$ Receptor Affinities

- **High Affinity**
  - Pimavanserin
  - Clozapine
  - Quetiapine
  - Aripiprazole

- **No Appreciable Affinity to $D2$**
  - Paliperidone
  - Lurasidone

- **Similar Affinities**
  - Risperidone
  - Brexipiprazole

- **Lower Affinity to $5$-$HT_2A$**
  - Cariprazine
# Evidence-Based Treatments for Parkinson’s Disease Psychosis

Prior to approval of pimavanserin.


## Efficacy Safety Practice Implications

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clozapine</strong></td>
<td>Efficacious</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Clinically useful</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>Unlikely efficacious</td>
<td>Unacceptable risk</td>
<td>Not useful</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td>Insufficient evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
</tbody>
</table>
Current Prescribing Practices in PD Psychosis and Non-PD Dementia Psychosis

<table>
<thead>
<tr>
<th>Antipsychotic Prescribing</th>
<th>PD Group (N=2597)</th>
<th>Non-PD Dementia Group (N=6907)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Dementia (n=793)</td>
<td>Without Dementia (n=1804)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Any AP Use</strong></td>
<td></td>
<td></td>
<td>451</td>
</tr>
<tr>
<td><strong>Any Typical AP</strong></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td><strong>High Potency</strong></td>
<td></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td><strong>Any Atypical AP</strong></td>
<td></td>
<td></td>
<td>437</td>
</tr>
<tr>
<td><strong>Quetiapine</strong></td>
<td></td>
<td></td>
<td>306</td>
</tr>
<tr>
<td><strong>Risperidone</strong></td>
<td></td>
<td></td>
<td>81</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td></td>
<td></td>
<td>41</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td></td>
<td></td>
<td>56</td>
</tr>
<tr>
<td><strong>Ziprasidone</strong></td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td><strong>Clozapine</strong></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Antipsychotics were prescribed in 50% of all the patients with PD and comorbid psychosis.

AP = antipsychotic.
Pimavanserin is a Selective Serotonin Inverse Agonist

- **Pimavanserin** binds to 5-HT$_{2A}$ receptors with a 5-fold higher selectivity over 5-HT$_{2C}$ receptors.

![Graph showing drug concentration vs response percentage](image)

- **Agonists:** Stimulate the receptor
- **Antagonists:** Block agonists but permit basal activity
- **Inverse Agonists:** Suppress basal activity

Pimavanserin 34 mg Reduced the Frequency and/or Severity of PD Psychosis, with Continued Improvement Over 6 Weeks*

*Mean SAPS-PD baseline score was 15.9 for pimavanserin and 14.7 for placebo. †Difference in change at Week 6 between the 2 arms was 3.06 points. SAPS-PD = Scale for the Assessment of Positive Symptoms adapted for Parkinson's disease.

Approximately 65% of Patients Taking Pimavanserin Experienced a $\geq 3$-Point Reduction in PD Psychosis

- Improvements in symptoms of psychosis were seen without worsening of motor function
- Hallucinations and Delusions improved
- 14% of patients had complete resolution of psychosis

N=185.
Complete response = SAPS-PD score reduced to 0 from baseline value. Patients with missing values were counted as non-responders.
Pimavanserin Safety Profile:
Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥ 2% and > Placebo

Percentage of Patients Reporting Adverse Reaction

<table>
<thead>
<tr>
<th></th>
<th>Pimavanserin 34 mg (N=202)</th>
<th>Placebo (N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Confusional state</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Hallucination</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

Adverse Reactions Leading to Discontinuation of Treatment

- Hallucination (2% pimavanserin 34 mg vs < 1% placebo)
- Urinary tract infection (1% pimavanserin 34 mg vs < 1% placebo)
- Fatigue (1% pimavanserin 34 mg vs 0% placebo)

Pimavanserin was not associated with increased sedation or increase in falls.

*Based upon placebo-controlled 6-week trials.

Pimavanserin Can Interact with Strong CYP3A4 Inhibitors and Inducers or with Drugs That Cause QT Interval Prolongation

### Strong CYP3A4 Inhibitors
- Concomitant use of pimavanserin with a strong CYP3A4 inhibitor increases pimavanserin exposure
- The recommended dose of pimavanserin when coadministered with strong CYP3A4 inhibitors (eg, ketoconazole) is 17 mg, taken orally as 1 tablet once daily

### Strong CYP3A4 Inducers
- Concomitant use of a strong CYP3A4 inducer may reduce pimavanserin exposure, resulting in a potential decrease in efficacy
- Patients should be monitored for reduced efficacy, and an increase in dosage may be needed if pimavanserin is used concomitantly with strong CYP3A4 inducers

### Concomitant Use with Drugs That Prolong QT Interval*
- Concomitant use of drugs that prolong the QT interval may add to the QT effects of pimavanserin and increase the risk of cardiac arrhythmias
- Avoid the use of pimavanserin in combination with other drugs known to prolong the QT interval

*In clinical trials, pimavanserin prolonged the QT interval (mean increase ~ 5–8 msec).
Antipsychotic Risks in “Dementia-Related Psychosis”

Black Box Warning
• Increased risk of cerebrovascular adverse events and mortality (1.7 ×) secondary to cardiovascular events and infections
• Issued for both typical and atypical antipsychotics
• Also type 2 diabetes, orthostatic hypotension, sedation, dry mouth, dizziness, constipation
Important Safety Information for Pimavanserin

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. [Pimavanserin] is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson’s disease psychosis.
Media Coverage of Pimavanserin

FDA worried drug was risky; now reports of deaths spark concern

By Blake Ellis and Melanie Hicken, CNN Investigates
Updated 6:00 AM ET, Mon April 9, 2018

FDA Repays Industry by Rushing Risky Drugs to Market

As pharma companies underwrite three-fourths of the FDA's budget for scientific reviews, the agency is increasingly fast-tracking expensive drugs with significant side effects and unproven health benefits.

by Caroline Chen, June 28, 5 a.m. EDT

Nuplazid, a drug for hallucinations and delusions associated with Parkinson's disease, failed two clinical trials. In a third trial, under a revised standard for measuring its effect, it showed minimal benefit. Overall, more patients died or had serious side effects on Nuplazid than after receiving no treatment.
Mortality in Parkinson’s Disease Psychosis

- Cox regression model adjusted to baseline age of 75 years
- Mortality for PD patients with (1) hallucinations with retained insight or (2) hallucinations or delusions without insight at baseline
  - 40% at 3 years
  - 80% at 7 years

Quetiapine

- Most prescribed antipsychotic for PD psychosis despite the lack of clinical efficacy data supporting its use
- Most movement disorders specialists and general neurologists find it to be effective in clinical practice
- Strong 5-HT$_2$A receptor antagonist and rarely worsens parkinsonism in doses of up to 100 to 200 mg/day. The usual starting dose is 25 mg qHS and this is slowly increased as needed (much lower than doses commonly used in psychiatry)
- Anti-histaminergic effect likely underlies the sedative effect. Psychosis in PD is commonly worse at night and sleep disruption almost universal in patients with advanced PD
  - Improvement in sleep quality and duration may be important
  - Reduction of caregiver stress when patient is sleeping
  - Risk of daytime sedation and increased falls and worsening of orthostatic hypotension in this vulnerable population

## Clinical Trials of Quetiapine

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Time</th>
<th>Dose Range</th>
<th>Average Dose</th>
<th>Number of Dropouts</th>
<th>Time to Dropout</th>
<th>UPDRS</th>
<th>BPRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shotbolt</strong></td>
<td>24</td>
<td>12 wks</td>
<td>25–150 mg</td>
<td>72.7 mg</td>
<td>16</td>
<td>Quetiapine patients dropped out faster than placebo patients</td>
<td>No Significant Effect</td>
<td>No Significant Effect</td>
</tr>
<tr>
<td><strong>Rabey</strong></td>
<td>58</td>
<td>12 wks</td>
<td>12.5 mg</td>
<td>119.2 mg</td>
<td>26</td>
<td>Not Used</td>
<td>No Significant Effect</td>
<td>No Significant Effect</td>
</tr>
<tr>
<td><strong>Ondo</strong></td>
<td>26</td>
<td>12 wks</td>
<td>50–200 mg</td>
<td>Not Given</td>
<td>5</td>
<td>Not Used</td>
<td>No Significant Effect</td>
<td>No Significant Effect</td>
</tr>
<tr>
<td><strong>Kurlan</strong></td>
<td>40 total (9 with PD psychosis)</td>
<td>10 wks</td>
<td>25–150 mg</td>
<td>120 mg</td>
<td>10</td>
<td>Not Used</td>
<td>No Significant Effect</td>
<td>No Significant Effect</td>
</tr>
</tbody>
</table>

BPRS = Brief Psychiatric Rating Scale.

Clozapine

• Very low D$_2$ affinity and high 5-HT$_{2A}$ affinity which results in no worsening of parkinsonism
• Most potent atypical antipsychotic and commonly used in high doses in refractory schizophrenia (eg, 400–800 mg/day)
• No worsening of parkinsonism and actually effective for parkinsonian tremor at ≤ 50 mg/day
• Results in dose-dependent improvement in levodopa-induced dyskinesia
• Highly effective in PD psychosis and highly underutilized due to need for CBC monitoring and concerns about agranulocytosis
  – Doses in PD psychosis usually < 50 mg/day starting at 6.25 mg qHS and titrating upward

# Clinical Trials of Clozapine

<table>
<thead>
<tr>
<th></th>
<th># of Patients</th>
<th>Time</th>
<th>Mean Dose</th>
<th>CGI P Value</th>
<th>SAPS P Value</th>
<th>BPRS P Value</th>
<th>UPDRS P Value</th>
<th>Positive PANSS P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCLOPS</strong></td>
<td>60</td>
<td>4 wks</td>
<td>24.7 mg</td>
<td>&lt;.001</td>
<td>.01</td>
<td>.002</td>
<td>.36</td>
<td>Not Used</td>
</tr>
<tr>
<td><strong>French Coop</strong></td>
<td>60</td>
<td>4 wks</td>
<td>35.8 mg</td>
<td>.001</td>
<td>Not Used</td>
<td>Not Used</td>
<td>.81</td>
<td>.0001</td>
</tr>
</tbody>
</table>

PSYCLOPS = PSYchosis and CLOzapine in the treatment of Parkinsonism; CGI = Clinical Global Impressions Scale; PANSS = Positive and Negative Syndrome Scale.  
Rapid Benefit and Dosing

- Appreciable improvement in a few days
  - Maximum improvement reached at 3 months
  - Mean doses 24 to 35 mg/day
  - Doses were kept under 50 mg/day
- 12-week open-label extension confirmed durable efficacy in both studies

Clozapine Adverse Effects

• Somnolence
• Postural hypotension
• Increased salivation
• Confusion
• Seizures
• Rare risk of agranulocytosis
• Cardiomyopathy
• Metabolic syndrome

Can Cholinesterase Inhibitors Improve Parkinson’s Disease Psychosis?

• Rivastigmine is indicated for treatment of PD dementia and reduces psychosis in this population

• Cholinesterase inhibitors also reduce psychosis in patients with dementia with Lewy bodies

• The cholinergic deficit in patients with PD or PD dementia is greater than that in Alzheimer’s disease

• It is reasonable to treat patients with PD dementia with cholinesterase inhibitors with or without psychosis. In clinical practice the antipsychotic efficacy of cholinesterase inhibitors in this population is quite mild and often inadequate when psychosis is troublesome and patients lack insight

Cholinesterase Inhibitors to Slow Progression of Visual Hallucinations in Parkinson’s Disease (CHEVAL)

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Delayed progression of minor VH to major VH without insight</th>
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<tbody>
<tr>
<td></td>
<td>Motor control, psychotic symptoms, cognitive impairment, mood disorders, daytime sleepiness, adverse events and compliance, disability, caregiver burden, and care use</td>
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<td>Cost effectiveness</td>
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<td>Functional brain networks</td>
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<tr>
<th>Study Design</th>
<th>Randomized double-blind, placebo-controlled, multicenter trial with economic analysis</th>
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<tr>
<th>Intervention</th>
<th>Rivastigmine 6 mg bid or placebo</th>
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| Primary Endpoint                                                          | Median time to progression from minor VH to major VH without insight                  |

ClinicalTrials.gov Identifier: NCT01856738.
Conclusions

• PD pathology predisposes to a variety of neuropsychiatric disorders including depression, anxiety, and dementia due to the multiple neurotransmitter systems affected

• PD psychosis is common and is associated with high morbidity and mortality

• Dopamine and serotonin abnormalities contribute to development of psychosis in PD
Conclusions

• Judiciously reducing non-PD medication that can interfere with cognition (eg, benzodiazepines) and selected other PD medications (especially anticholinergics and amantadine) may improve psychosis, but over-reduction of medication can worsen parkinsonism

• Antipsychotic medication targeting $5\text{-HT}_{2A}$ receptors can improve PD psychosis without compromising motor function