PSYCHOSIS: CHALLENGING ISSUES IN PARKINSON’S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS
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 and Alzheimer's dementia
The Challenge of Parkinson's Disease Psychosis:

I Really Want to Block D2 But I Can’t
Organization of the Striatum

DORSOLATERAL
Lateral Putamen
FUNCTION: Motor

DORSOMEDIAL
Anterior Caudate
FUNCTION: Associative

VENTROMEDIAL
Nucleus Accumbens
FUNCTION: Limbic

Associative striatum: increased D2 postsynaptic activity associated with positive symptoms of psychosis (hallucinations, delusions, disorganized thoughts or behavior)
Dopamine D2 Antagonism in the Nigrostriatal Pathway


Extrapyramidal Symptoms (EPS)
Clinical Symptoms and Time Course of Parkinson’s Disease

- Pre-motor/prodromal period
  - Parkinson’s disease diagnosis
- Early
  - Bradykinesia
  - R rigidity
  - Tremor
- Advanced/late
  - Fluctuations
  - Dyskinesia
  - Psychosis
- Motor
  - Dysphagia
  - Postural instability
  - Freezing of gait
  - Falls
- Non-motor Complications
  - Urinary symptoms
  - Orthostatic hypotension
  - Dementia
  - Fluctuations
  - Dyskinesia
  - Psychosis

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

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

Stages in the Evolution of PD-related Pathology

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

Patients With PD and Visual Hallucinations Have Increased 5HT2A Receptor Binding

Psychosis Can Result From Overactivation of Both Dopaminergic and Serotonergic Signaling

**Psychosis can result from overaction of the mesolimbic dopamine pathway**


**Hallucinations can result from activation of 5HT2 receptors**

VTA: ventral tegmental area; DA: dopamine.

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

**Symptoms**¹
- Requires the presence of at least 1 of the following symptoms:
  - Hallucinations
  - Delusions
  - Illusions
  - False sense of presence

**Associated features**¹
- May occur with or without:
  - Insight
  - Dementia
  - Parkinson’s disease Tx

- Must occur in patients with previously diagnosed PD
- Must be recurrent or continuous for at least 1 month

**Diagnosis of PDP**

**Other causes excluded**¹,²

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

---

NINDS: National Institute of Neurological Disorders and Stroke
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
  - Other sensory modalities (e.g., tactile, olfactory) are even rarer

• 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

Impact of PDP

- Increased caregiver burden
- Increased mortality
- Increased nursing home placement

Case-control study compared motor disability, dementia, and prevalence of hallucinations in nursing home PD patients with 2 community subjects matched for age, gender, and PD duration

- No difference in any measure EXCEPT 82% of nursing home subjects reported hallucinations compared to 5% of those living in the community

PDP Treatment
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 [Vesicar])

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

Clozapine D2 and 5HT2 Occupancy

## Atypical Antipsychotics Ki

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>5HT2A</th>
<th>M1</th>
<th>H1</th>
<th>α1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>1.6*</td>
<td>8.7</td>
<td>&gt; 1000</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1.35</td>
<td>0.07</td>
<td>&gt; 1000</td>
<td>1.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Clozapine</td>
<td>158</td>
<td>5.35</td>
<td>6.17</td>
<td>1.13</td>
<td>7.0</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>6.3</td>
<td>5.6</td>
<td>&gt; 1000</td>
<td>12.3</td>
<td>0.31 (α1)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>1.0</td>
<td>0.47</td>
<td>&gt; 1000</td>
<td>&gt; 1000</td>
<td>48 (α1A)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>31</td>
<td>3.73</td>
<td>2.5</td>
<td>2.19</td>
<td>263</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>4.2</td>
<td>0.71</td>
<td>&gt; 1000</td>
<td>20</td>
<td>0.70</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3.25</td>
<td>0.17</td>
<td>&gt; 1000</td>
<td>18.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>379</td>
<td>636</td>
<td>371**</td>
<td>6.9</td>
<td>39</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>6.85</td>
<td>0.60</td>
<td>&gt; 1000</td>
<td>63</td>
<td>9.0</td>
</tr>
</tbody>
</table>

* D2 partial agonist  ** Metabolite norquetiapine has M1 Ki 38 nM
### Double-Blind Atypical Antipsychotic Trials for the Treatment of PDP

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Effects on Psychosis</th>
<th>Effects on Motor Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>60</td>
<td>+++</td>
<td>+  *</td>
</tr>
<tr>
<td>Clozapine</td>
<td>60</td>
<td>+++</td>
<td>+  *</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>160</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>15</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>58</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>16</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

* Improved motor function

Antipsychotic-Associated Mortality in Parkinson's Patients With Dementia (n=15,332)

Hazard Ratio of Death Among Antipsychotic Users

HR 2.35 (95% CI 2.08-2.66; P < .001)
- Olanzapine 2.79 (95% CI, 1.97-3.96)
- Risperidone 2.46 (95% CI, 1.94-3.12)
- Quetiapine 2.16 (95% CI, 1.88-2.48)

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 (α1)

Can 5HT2A Antagonists Without D2 Activity Have Antipsychotic Effects?
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 Info

• Pharmacokinetics\(^1\)
  • 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\(^1\)
  • CYP3A4 is the major enzyme responsible for pimavanserin metabolism
    • Recommend 50% dose reduction when used with strong 3A4 inhibitors

Simulation of a typical concentration profile following daily dosing with 17 mg and 34 mg \(^2\)

2. ACADIA Pharmaceuticals Inc. NUPLAZID sponsor background information. Presented at: Meeting of the Psychopharmacologic Drugs Advisory Committee; March 29, 2016.
The Challenge of Treating Dementia Related Psychosis:

*Is My Treatment Going to Be Fatal?*
Cumulative Incidence of Tardive Dyskinesia (TD) With Conventional Neuroleptics

TD With Haloperidol or Risperidone in the Elderly*

*Mean age, 66 years; patients with schizophrenia, dementia, mood disorders, psychotic symptoms, or severe behavioral disturbances.
†P < 0.05 vs. haloperidol.

The First Warning: Cerebrovascular Adverse Events (CVAE)

• 2002-2003 data emerged about increased risk of CVAE in studies of dementia-related psychosis, first with risperidone, and then olanzapine and aripiprazole

• August 2003: **First FDA Label Change:**

*Warning: Cerebrovascular Adverse Events in Elderly Patients With Dementia*

• Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis

• In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo

• Risperidone is not approved for the treatment of patients with dementia-related psychosis
CVAE and Antipsychotics: Issues

a. None of the dementia studies were designed to evaluate the risk of CVAE
   - Patients were not stratified by CVAE risk factors

b. Lack of plausible mechanisms
   - **Orthostatic Hypotension**: Analyses on the relationship between orthostatic hypotension and CVAEs did not show a consistent relationship in risperidone trials.
   - **Prothrombotic Effects**: In vitro evaluation of risperidone and 9-OH risperidone on:
     - **Platelets**: No effects on platelet shape change, adhesion, and aggregation
     - **Coagulation**: No increases of PT, PTT, and thrombin time
     - **Fibrinolysis**: No effects on whole blood clot lysis

Atypical Antipsychotics and Risk of Cerebrovascular Accidents

Crude Stroke Rate per 1000 Person-Years*

* No significant difference

## Early Trials of Atypical Antipsychotics in Patients With Dementia

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Trial</th>
<th>N</th>
<th>Mean Age (yrs)</th>
<th>Duration (wks)</th>
<th>Efficacy Results (vs Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Katz et al</td>
<td>625</td>
<td>83</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>344</td>
<td>81 (median)</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>Brodaty et al</td>
<td>337</td>
<td>83</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Satterlee et al</td>
<td>238</td>
<td>Not available (≥65)</td>
<td>8</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Street et al</td>
<td>206</td>
<td>83</td>
<td>6</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>De Deyn et al</td>
<td>652</td>
<td>77</td>
<td>10</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Tariot et al</td>
<td>284</td>
<td>84</td>
<td>10</td>
<td>Improved agitation but not psychosis</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>De Deyn et al</td>
<td>208</td>
<td>82</td>
<td>10</td>
<td>Inconsistent†</td>
</tr>
</tbody>
</table>

## Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease (CATIE-AD)

### Table 1. Baseline Characteristics of Patients Who Underwent Randomization. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Olanzapine Group (N=100)</th>
<th>Quetiapine Group (N=94)</th>
<th>Risperidone Group (N=85)</th>
<th>Placebo Group (N=142)</th>
<th>Total (N=421)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>78.8±7.3</td>
<td>77.3±8.7</td>
<td>78.4±7.1</td>
<td>77.3±7.1</td>
<td>77.9±7.5</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>55 (55)</td>
<td>50 (53)</td>
<td>49 (58)</td>
<td>81 (57)</td>
<td>235 (56)</td>
</tr>
<tr>
<td>Race — no./total no. (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80/99 (81)</td>
<td>76/94 (81)</td>
<td>68/85 (80)</td>
<td>107/141 (76)</td>
<td>331/419 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>14/99 (14)</td>
<td>15/94 (16)</td>
<td>15/85 (18)</td>
<td>31/141 (22)</td>
<td>75/419 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>5/99 (5)</td>
<td>3/94 (3)</td>
<td>2/85 (2)</td>
<td>3/141 (2)</td>
<td>13/419 (3)</td>
</tr>
<tr>
<td>Education — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not complete high school</td>
<td>28 (28)</td>
<td>21 (22)</td>
<td>15 (18)</td>
<td>37 (26)</td>
<td>101 (24)</td>
</tr>
<tr>
<td>General equivalency diploma or high-school diploma</td>
<td>35 (35)</td>
<td>33 (35)</td>
<td>28 (33)</td>
<td>46 (32)</td>
<td>142 (34)</td>
</tr>
<tr>
<td>&lt;4 yr of college</td>
<td>16 (16)</td>
<td>16 (17)</td>
<td>22 (26)</td>
<td>36 (25)</td>
<td>90 (21)</td>
</tr>
<tr>
<td>≥4 yr of college</td>
<td>15 (15)</td>
<td>21 (22)</td>
<td>17 (20)</td>
<td>20 (14)</td>
<td>73 (17)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (6)</td>
<td>3 (3)</td>
<td>3 (4)</td>
<td>3 (2)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>MMSE total score</td>
<td>15.0±5.4</td>
<td>14.9±6.1</td>
<td>15.7±6.1</td>
<td>14.7±5.8</td>
<td>15.0±5.8</td>
</tr>
</tbody>
</table>
CATIE-AD: Drop-Outs Due to Inefficacy or Intolerability

The Next Warning: Mortality

• 2004: Data emerged about increased risk of mortality in studies of dementia-related psychosis. First warnings were for atypicals.

• 2005: **Meta-analysis published:**¹ 15 trials of 10-12 weeks in duration, including 16 contrasts of atypical antipsychotic drugs with placebo met criteria (aripiprazole [n=3], olanzapine [n=5], quetiapine [n=3], risperidone [n=5]).

  **Sample size:** 3353 randomized to study drug, 1757 were randomized to placebo.

  **Findings:**    a. There were no differences in dropouts.

    b. Death occurred more often among patients randomized to drugs: 3.5% (n=118) vs 2.3% (n=40); **OR 1.54 (95% CI: 1.06-2.23; P=.02).**

    c. Risk difference was 0.01 (95% CI, 0.004-0.02; P=.01). **NNH: 100**

    d. Sensitivity analyses did not show evidence for differential risks for **individual drugs**, severity, sample selection, or diagnosis.

The Next Warning: Mortality

- Data were available from the 2 studies comparing haloperidol with risperidone, and one vs quetiapine, and these were combined.
- There were 15 deaths (6.2%) with haloperidol and 9 (3.8%) with placebo among 243 patients receiving haloperidol and 239 patients receiving placebo.
- Risk for death was calculated as an **OR of 1.68** (95% CI, 0.72-3.92; P=.23).

Mortality Risk Among Psychotropics in Elderly Patients With Dementia

Retrospective analysis of mortality risk in 90,786 veterans ages 65 years or older with a diagnosis of dementia and > 180 days of follow-up.

Died Within 180 Days

Mortality Risk Among Psychotropics in Elderly Patients With Dementia

Retrospective analysis of mortality risk in 90,786 veterans ages 65 years or older with a diagnosis of dementia and > 180 days of follow-up.

Number Needed to Harm

Mortality Risk Among Psychotropics in Elderly Patients With Dementia

Retrospective analysis of mortality risk in 90,786 veterans ages 65 years or older with a diagnosis of dementia and > 180 days of follow-up.

Mortality Risk Among Psychotropics in Elderly Patients With Dementia

Retrospective analysis of mortality risk in 90,786 veterans ages 65 years or older with a diagnosis of dementia and > 180 days of follow-up.

Increased risk of mortality

Decreased efficacy
Are There Any ‘Safe’ Evidence Based Treatments for Psychosis or Agitation in Dementia

- **Behavioral and Environmental**: Treat pain (even if patient can't express it), ensure adequate vision (including lighting), hearing, extensive staff training in behavioral approaches.

- **Acetylcholinesterase inhibitors**: strong evidence points to the benefits of AChEIs for neuropsychiatric symptoms of mild to moderate AD. Memantine has also shown evidence of efficacy both as monotherapy and when combined with AChEIs.

- **Lamotrigine (but not VPA or carbamazepine)**: Anticonvulsants show efficacy in violent TBI pts, yet the evidence in dementia is largely negative, aside from small case series and open-label studies. Multiple RCTs for valproate have shown no efficacy. Data for carbamazepine are conflicting but tolerability and kinetic concerns limit its use. **One 16-week lamotrigine** trial in 40 inpatients showed modest benefit from low doses (mean endpoint dose 46.3 ± 24.4 mg/d, range 25–100 mg/d) to the extent that the doses of concomitant antipsychotics could be lowered.

- **SSRIs**: In addition to AChEIs, the only other medication class with significant positive results in aggressive dementia patients (includes low dose trazodone).

Citalopram for Agitation in Alzheimer’s Disease (CitAD Study)

• **Rationale:** SSRI antidepressants have shown efficacy for agitation in dementia patients, and lack some of the safety concerns for other medication classes.

• **Design:** Participants with probable Alzheimer’s disease (n = 186) were randomized to receive a psychosocial intervention plus double-blind citalopram (n = 94) or placebo (n = 92) for 9 weeks. Citalopram started at 10 mg/d with planned titration to 30 mg/d over 3 wks based on response and tolerability.

• **Primary outcome measures:** Neurobehavioral Rating Scale agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC).
  - Secondary outcomes: Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI), ADLs

THE GOOD

Neurobehavioral Rating Scale agitation subscale:
- Week 9: Mean citalopram group score: 4.1 ± 3.0 vs 5.4 ± 3.2 for placebo
- Significance: P = .01; effect size: 0.41

Modified Alzheimer Disease Cooperative Study-CGI of Change
- 40% of citalopram arm were much or very much improved vs 26% of the placebo group.
- OR of being at or better than a given CGIC category: 2.13 (95%CI, 1.23-3.69; P = .01)

Citalopram showed significant improvement on the CMAI, total NPI, and caregiver distress scores but not on the NPI agitation subscale, ADLs, or in less use of rescue lorazepam.

CitAD Study Outcomes

THE BAD

Worsening of cognition (−1.05 MMSE points; 95% CI, −1.97 to −0.13; P = .03) and QT interval prolongation (18.1 ms; 95%CI, 6.1-30.1; P = .01) were seen in the citalopram group.

CitAD Secondary Analysis

Predictors of outcome: 5 covariates were likely predictors: setting, cog impairment, degree of agitation, age, use of lorazepam

Citalopram more effective: outpatients, less cognitive impairment, have moderate agitation, and be within the middle age range (76–82 years).

Placebo more effective: more likely to be in long-term care, have more severe cognitive impairment, have more severe agitation, and be treated with lorazepam.

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.
Summary - Dementia

1. Traditional antipsychotics have shown efficacy for psychosis in dementia, but come with two significant warnings:
   • Cerebrovascular adverse events (i.e., stroke)
   • Mortality

2. There is currently no approved agent for dementia related psychosis, though trials of pimavanserin are ongoing.

3. The AChEIs and SSRI antidepressants have demonstrable efficacy for agitation in Alzheimer’s dementia with fewer safety concerns than for antipsychotics