Schizophrenia and other Psychotic Disorders in the Elderly

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PROVIDENCE VAMC
Objectives

- Clinical Evaluation of Late Life Psychosis
- Appreciate the differential diagnosis of LLP
- Know the medical work up of LLP
- Understand first-line treatment options for the most common causes
General Considerations in Late Life Psychosis

Range 10-62% in nursing home population
Up to 27% in outpatient psychiatry patients
23% lifetime risk

Holroyd, 1999; Webster 1998
Phenomenology

Delusions
Vague/poorly formed/fleeting suspicions
Intricate (systematized)

Hallucinations
Illusions
Name being called
Multiple well-formed Running commentary
Phenomenology

Psychotic Symptoms

Primary Psychotic Disorder

Secondary Psychotic Disorder
SECONDARY >> PRIMARY CAUSES

>1700 pts consecutively admitted to a geri psych unit
140 geriatric patients in outpt. psychiatry

(Holroyd, 1999)
A 69 year old female with a history of DM and HTN presents to your office for a routine visit. She is more disheveled than usual and has lost some weight. On further questioning you learn that she has become agitated by her neighbors who she believes have been harassing her by intentionally making noise to bother her which she hears through the ceiling.

WHAT ELSE WOULD YOU WANT TO KNOW?
Is this psychosis or just thin walls?

- From patient’s perspective
  - Explore patient’s beliefs with an open non-judgmental curiosity
  - No matter how bizarre try to see it from their perspective
    - Systematized vs. vague
    - How strongly does she believe this
    - How long have the neighbors been bothering her?
- Do you need input from a caregiver or relative?
IS COGNITION AFFECTED?

ARE SUBSTANCES/MEDICATIONS INVOLVED?

IS THERE A MOOD DISORDER?

IS THERE A PREMORBID PERSONALITY DISORDER OR PAST PSYCH HX?
**Time course is crucial**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>Drugs, alcohol, toxins</td>
<td>Days to months</td>
</tr>
<tr>
<td>Disease</td>
<td>Days to months</td>
</tr>
<tr>
<td>Depression and other affective disorders</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>Dementia</td>
<td>Months to years</td>
</tr>
<tr>
<td>Delusional disorder and schizophrenia-spectrum disorders</td>
<td>Months to decades</td>
</tr>
</tbody>
</table>
You learn that she can hear their voices through the ceiling and that they are commenting on her actions. You also learn that she believes that her next door neighbor is intentionally disrupting her hot water supply because he does not want her to take showers in the early am. She also believes that the neighbor is attacking her furniture with an ice pick when she is out.

She does not have depressive symptoms. Her physical exam is normal. Her cognition is intact.

What medical conditions can cause psychosis and should be ruled out?
What is the medical work up of initial psychosis in late life?

- Chemistry panel to evaluate for disturbances in fluid or electrolytes
- Complete blood count to evaluate for infectious processes; blood culture if indicated
- Hepatic function panel to evaluate for liver abnormalities
- Thyroid-stimulating hormone level to rule out thyroid disease
- Serum treponemal test such as fluorescent treponemal antibody absorption (FTA-ABS) to screen for syphilis
- Urinalysis to evaluate for urinary tract infection or other abnormalities; urine culture if indicated
- Urine drug screen to evaluate for recent substance use
- Vitamin B12 levels to evaluate for deficiency
- HIV to evaluate for infection
Additional Tests to Consider Based on History

- **Computed tomography (CT) brain or magnetic resonance imaging (MRI)** to evaluate for space-occupying lesions, demyelinating disorders, or stroke
- **Electroencephalogram (EEG)**
- **Lumbar puncture**
- **Heavy metal screen**
- **Rheumatologic workup** (e.g., antinuclear antibody, antiribosome antibody, anti-NMDA receptor antibody)
You learn that she can hear their voices through the ceiling and that they are commenting on her actions. You also learn that she believes that her next door neighbor is intentionally disrupting her hot water supply because he does not want her to take showers in the early am. She also believes that the neighbor is attacking her furniture with an ice pick when she is out.

She does not have depressive symptoms. Her physical exam is normal. Her cognition is intact.

Lab w/u is negative and imaging is wnl. What is the differential?
Psychotic Syndrome vs Symptoms

- **Full Syndrome=Schizophrenia**
  - Long-standing... > 6 months
  - Keeps company with other symptoms
    - Delusions
    - Hallucinations
    - Negative symptoms
    - Disorganized behavior
    - Disorganized speech

- **Partial Syndrome=Delusional Disorder**

- **Symptoms**
  - Delusions/hallucinations
Scz: Nosology

- Feighner Criteria: < 40
- DSM III: < 45
- DSM III-R: > 45 Late-onset type
- DSM IV: No age restrictions

Howard, 2000
Schizophrenia over the lifespan

Early Onset

Age 40

Late Onset

Age 60

VLOP

20-36%
W>M
Well organized and persecutory delusions
Visual, tactile, olfactory hallucinations
Lower doses of neuroleptic necessary

FH 10-15% in both groups
Risk factors the same

Maglione, 2014
Very Late-Onset Schizophrenia-like Psychosis

Distinguishing factors:
- Lower genetic load
- Less early childhood maladjustment
- Less thought disorder and less negative symptoms
- More likely a neurodegenerative process, rather than neurodevelopmental
- Greater risk for tardive dyskinesia

Differential diagnosis includes disorders that are not schizophrenia:
- Psychosis of dementia
- Psychosis secondary to general medical conditions or substance use
- Mood disorder with psychotic features
- Delusional disorder
- Unspecified etiology

Howard 2000
Delusional Disorder

- Delusions without prominent auditory or visual hallucinations
  - Persecutory, somatic, erotomanic, grandiose, or jealous
- Basic personality, occupational and intellectual features are preserved. Social functioning is compromised.
- Average age of onset
  - 40-49: Male
  - 60-69: Female
- Risks
  - FH of schizophrenia or cluster A personality d/o
Risperidone vs Olanzapine in late life Schizophrenia

- Largest RCT to date. International, double-blind, 8-week RCT
- 176 patients, aged >60 years with schizophrenia or schizoaffective disorder
- Randomly assigned to flexible doses of Risperidone (1-3; median 2 mg/d) or Olanzapine (5-20; median 10 mg/d)
- Both antipsychotics produced significant improvement from baseline scores on PANSS
- No significant difference between the two drugs on psychopathology ratings, cognitive skills, QTc, EPS reports, or anticholinergic side effect reports
- Greater weight gain with olanzapine (p=.05)
Schizophrenia: Treatment

- Maintenance pharmacotherapy is usually required d/t risk of relapse
- Higher risk of adverse antipsychotic effects → starting and maintenance dose is much lower than usual doses in younger adults
- Patients with LOS respond well to lower doses
  - Approx 50% of dose needed by patients with EOS and
  - 25-33% of the dose used in younger patients with SCZ
Recommended Dosages in Older Patients with Schizophrenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial (mg/day)</th>
<th>Typical Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>0.25-0.5</td>
<td>1-3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5</td>
<td>5-15</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-25</td>
<td>75-200</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2-5</td>
<td>5-20</td>
</tr>
<tr>
<td>*Clozapine</td>
<td>6.25-12.5</td>
<td>50-150</td>
</tr>
</tbody>
</table>

*Clozapine, though gold standard for treatment resistant schizophrenia, is infrequently prescribed due to side effect limitations (hypotension, anticholinergic effects, agranulocytosis).
Dose Reduction for LLS

- Antipsychotic dose can be successfully reduced in more than 80% of patients with stable LLS.
- The mean D2/3R occupancy of the entire sample decreased from 70% (12%) to 64% (12%) after a mean antipsychotic dose reduction of 34.6% (3.4%).
- The dose reduction improved adverse effects (EPS, hyperprolactinemia)
- And improved clinical symptoms

Graff-Guerrero, 2015
Long-Term Side Effects of Atypical Antipsychotics in OLDER PATIENTS

- Weight gain
- Type 2 diabetes mellitus
- Hyperlipidemia
- Hyperprolactinemia
- Cardiac conduction disorders
- TD, EPS
- Strokes (in dementia patients)
- Increased mortality (in dementia patients)

- FDA Warnings:
  - In all age groups: weight gain, diabetes, hyperlipidemia
  - In dementia patients: stroke and mortality
Psychosocial THERAPIES—Late-Life Schizophrenia

- Cognitive Behavior Social Skills Training - CBSST
  - >45yo with schizophrenia or schizoaffective dx

- Helping Older People Experience Success - HOPES
  - >50yo with serious mental illness, more than half with schizophrenia or schizoaffective dx

- Functional Adaptation Skills Training - FAST
  - >40yo with schizophrenia or schizoaffective dx

- All demonstrated benefit
- None specifically studied late-onset schizophrenia

Granholm 2013, Mueser 2010, Bartels 2013, Patterson 2006
Mrs. A is a 72 y/o W with a h/o paranoid schizophrenia treated with risperidone 3mg po qhs. + h/o diabetes (under good control) and CAD. She has been living at a NH x 2 years, doing well.

Pharmacy review recommended her risperidone be tapered and discontinued.

Risperidone was tapered over a three month period. 2 weeks after d/c’ing it she became agitated and withdrawn with vivid hallucinations.

Emergently hospitalized with subsequent resumption of former dose and good sx. control.
CASE #2

- An 81 y/o male has been seeing his dead wife and dead sister x 3 months. He sometimes talks to them, and he says they sometimes respond to him. He has a 4-yr h/o declining memory and ADLs. He has a history of depression and currently manifests some depressive sx. There is no h/o etoh or substance abuse. MMSE=17/30. On physical exam, he has an elevated bp (165/90), increasing rigidity in his UE in response to progressively more rapid movement and a shuffling gait. He has no tremors or other neuro. abnormalities. Lab tests were normal and CT showed mild cortical atrophy.

Cohen, 2013
Case #2

What is the most likely explanation for his symptoms?
1. Lewy Body Dementia
2. Late-onset schizophrenia
3. Alzheimer’s Disease
4. Depression with Psychotic Features
5. Parkinson’s Disease with dementia
Case #2

- What is the most likely explanation for his symptoms?
  1. Lewy Body Dementia
  2. Late-onset schizophrenia
  3. Alzheimer’s Disease
  4. Depression with Psychotic Features
  5. Parkinson’s Disease with dementia
No psychosis

With psychosis

1 year: 26%
2 years: 36%
3 years+: 50%

More agitation
Faster decline
More caregiver distress
Faster institutionalization

? Independent risk factor for death

Jeste, 2000, Paulson, 2000
Compared with non psychotic AD:
Changes > in PFC than MTL

- Decreased gray matter thickness
- Higher tau burden
- Greater glucose hypometabolism
- Greater synaptic loss

May be genetically determined
AD with Psychosis (AD+P)

- Three subtypes of psychotic symptoms
  - Misidentification Syndromes (Forstl, 1991)
    - Phantom boarder syndrome
    - Caregiver is an imposter
    - Mirror image
  - Paranoid Delusions
    - People are stealing things, that they are in danger
    - Infidelity
    - Abandonment
  - Hallucinations (V>A)
    - People from the past, intruders, animals.

? Cognitive problem
Non-pharmacologic tx of Psychotic Symptoms

- Most importantly do a good assessment of the symptoms
  - Antecedents, surrounding factors, consequences
  - Who is bothered by the sx?
  - Is there is sensory deprivation? → Fix this
  - Education re: natural course

- Rule out other causes of psychosis
  - Depression/delirium

Cohen-Mansfield, 2003
Non-pharmacologic tx of Psychotic Symptoms

• Assess for environmental interventions
  ○ Reassurance, redirection, change of staffing, modify routines
  ○ Stimulation oriented therapies: day program

• Caregivers as imposters
  ○ Focus on improving relationships with caregivers
    ▶ Re-introduce caregivers each time
    ▶ Educate caregivers re: effects on memory

• People stealing
  ○ Purchase multiple items such as reading glasses
  ○ Help patient to always put in the same place

Cohen-Mansfield, 2003
Pharm: Treatment of Psychosis

- Increased risk of mortality/morbidity
  - 1.6–2.0 RR in the subsequent 12–52 weeks
  - Sedation, orthostasis, falls

- Use non-pharm or other pharm tx unless there is very significant distress or risk of harm to patient or others.

- Discuss risks with family thoroughly and document

CATIE-AD Study
ATYPICAL ANTIPSYCHOTIC EFFECTIVENESS

- 42-site, double-blind, placebo-controlled trial that included 421 outpatients with Alzheimer’s disease and psychosis, aggression, or agitation.

- Randomly assigned to receive flexible dosing of olanzapine (mean dose, 5.5 mg per day), quetiapine (56.5mg/day), risperidone (1.0mg/day), or placebo for up to 36 weeks. At any time after two weeks treatment, the initially assigned medication could be switched to an alternative treatment because of insufficient efficacy, adverse effects, or other reasons, based on the clinical impression of the blinded treating clinician.

- Time to discontinuation for any reason was the primary outcome, and there was no difference between antipsychotic and placebo treatment groups. An analysis of clinical symptoms found that at the last observation on the initially assigned drug, those treated with olanzapine or risperidone had improved more than those treated with placebo on global behavioral measures. The magnitude of improvement was greatest on the BPRS hostile suspiciousness factor, a measure of anger, aggression, and paranoia.

- On the BPRS psychosis factor, only risperidone showed benefit compared to placebo. Antipsychotic treatment did not benefit daily functioning, care needs, or quality of life, compared to placebo.
CATIE-AD: All-cause Discontinuation
PHASE 1

Proportion Remaining on Initially Assigned Drug

Time (weeks)

Olanzapine (N=99)  Quetiapine (N=94)  Risperidone (N=84)  Placebo (N=139)

<table>
<thead>
<tr>
<th></th>
<th>OLZ</th>
<th>QTP</th>
<th>RIS</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>99</td>
<td>94</td>
<td>84</td>
<td>139</td>
</tr>
<tr>
<td>Discontinued (%)</td>
<td>80</td>
<td>82</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>50th percentile (week)</td>
<td>8.1</td>
<td>5.3</td>
<td>7.4</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Cox proportional hazards, \( P=.52 \)
## Antipsychotic Discontinuation IN AD
### ADAD TRIAL

<table>
<thead>
<tr>
<th>Phase A</th>
<th>Phase B</th>
</tr>
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<tbody>
<tr>
<td>Open Treatment</td>
<td>Randomized Trial</td>
</tr>
<tr>
<td>16 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td>I---Risperidone</td>
<td>I---Risperidone---I---</td>
</tr>
<tr>
<td>I-Risperidone---I</td>
<td>I---Risperidone---I------Placebo-----I</td>
</tr>
<tr>
<td>I------Placebo------I</td>
<td>I------Placebo------I</td>
</tr>
</tbody>
</table>

- N=180
- Mean dose 0.97mg/d
- 110 responders randomized
- Relapse, first 16 weeks:
  - 60% P, 33% Risperidone
- Relapse, second 16 weeks:
  - 48% P, 15% Risperidone
- Adverse effects: No substantial difference

![Graph showing primary endpoint](graph.png)

Devanand 2012
Atypical Antipsychotic Efficacy FOR PSYCHOSIS IN AD

Aripiprazole
Breden, 2004/Mintzer, 2007, 2.5, 10 mg
De Deyn, 2003, 3 to 15 mg
Streim, 2004/Streim, 2008, mean 66 mg
Subtotal (I-squared = 60.8%, p = 0.078)
Overall Effect Size = 0.11

Olanzapine
De Deyn, 2004, 1.25, 5, 7.5 mg
Debert, 2005, 5.2 mg
Kennedy, 2005, 2.5 to 7.5 mg
Schneider, 2006/Sultzer, 2008, 5.5 mg
Street, 2000, 5, 10, 15 mg
Subtotal (I-squared = 14.7%, p = 0.321)

Quetiapine
Schneider, 2006/Sultzer, 2008, 56.5 mg
Tariot, 2002, 25-600 mg
Zhong, 2004/Zhong, 2007, 100, 200 mg
Subtotal (I-squared = 61.6%, p = 0.138)

Risperidone
Brodaty, 2003/Brodaty, 2005, 1 mg
Debert, 2005, 1 mg
Katz, 1999, 0.5, 1, 2 mg
Mintzer, 2006, 0.5 to 2.5 mg
Schneider, 2006/Sultzer, 2008, 1 mg
Subtotal (I-squared = 55.0%, p = 0.064)

NOTE: Weights are from random effects analysis

Favors Placebo * Favors Treatment
Principles of pharmacotherapy

- Identify target symptoms
- Benefit should occur in first 4 weeks, if no benefit at reasonable dose, d/c med.
- Try a dose reduction at 3 months weighing r/b
- There is dose/harm relationship

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STARTING DOSE</th>
<th>TARGET DOSE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2.5-5 mg/day</td>
<td>7-12 mg/day</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5-5 mg/day</td>
<td>5-10 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>12.5-25 mg/day</td>
<td>50-200 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25-0.5 mg/day</td>
<td>0.5-1.5 mg/day</td>
</tr>
</tbody>
</table>
SSRI’s

Original Investigation
Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

QT prolongation and cognitive effects at tested dose of 30mg.
Unclear benefit at lower dose

Porsteinsson, 2014
Psychosis and Parkinson’s Disease

- Psychosis in 20-40% of patients
- “Benign Hallucinosis”
  - Non-troubling mild perceptual disturbances, + insight, no need for tx.
  - Sensation of a presence or sideways passage
  - VH: People, animals, inanimate objects
  - Evening hours when there is low stimulation
  - Last seconds to minutes
  - Non-threatening

VS
- Frightening complex psychotic sx, no insight, and tx is necessary.
- Persecutory delusions + VH+- delirium

Zahodne, LB 2008; Weintraub, 2007
Causes of Psychosis in PD

ACH

Lewy bodies in the amygdala and parahippocampus

DA deficiency at level of the retina

Structural deficits

RBD

REM intrusion

DA agonists

Zahodne, LB 2008
Psychosis in PD: Principles of Tx

- Evaluate for other causes
  - Dehydration, electrolyte abnormalities, infection, subdural hemorrhage
- Reduce PD medications
- Trial of CHE-I $\rightarrow$ Rivastigmine first line
- Antipsychotic $\rightarrow$ clozapine
- Pimavanserin: new option recently approved. 5HT2A inverse agonist
Antipsychotics for the management of psychosis in Parkinson’s disease: systematic review and meta-analysis

Fig. 4 Random effects meta-analysis of the use of quetiapine in the management of Parkinson's disease psychosis, efficacy measure: BPRS.

Fig. 8 Random effects meta-analysis of the use of clozapine in the management of Parkinson's disease psychosis, efficacy measure: CGI.
Pimavanserin for patients with Parkinson’s disease psychosis: a randomised, placebo-controlled phase 3 trial

- 6 week randomized double blind trial
- patients with PD with psychosis age > 40 years
- AP not permitted during the study
- outcome: ap benefit SAPS-PD= Parkinson's Disease adapted scale for the assessment of positive sx
- 199 patients
- 5.79 dec in SAPS c/w PBO decrease of 2.73
- No worsening of motor function
Case #3

- An 80 y/o woman reports hallucinations of children and small animals when she is alone in her room. She sometimes becomes disturbed and agitated by these hallucinations. Her family notes that she is having more difficulty walking and at times has hand tremors when she sits quietly. She has a 9 month history of short-term memory loss, word-finding difficulties, and difficulties with paying bills and preparing meals for her spouse and herself. Examination is unremarkable except for cogwheel rigidity and resting tremors.
Case #3

Which of the following is the most likely diagnosis?

1. Dementia with Lewy Bodies
2. Alzheimer’s Disease
3. Parkinson’s Disease with dementia
4. Huntington’s Disease
Case #3

● Which of the following is the most likely diagnosis?
  1. Dementia with Lewy Bodies
  2. Alzheimer’s Disease
  3. Parkinson’s Disease with dementia
  4. Huntington’s Disease
Lewy Body Dementia

• Primary symptoms
  o (a) Parkinson’s-like movement changes, including slowness, stiffness, tremor, or balance problems;
  o (b) Visual hallucinations, often of small people, children, or animals;
  o (c) Spontaneous changes in alertness, concentration, and attention, called cognitive fluctuations;

• Supporting symptoms
  o (d) A sleep disorder causing people to “act out” their dreams, called rapid eye movement behavior disorder (RBD).
  o (e) Neuroleptic Sensitivity
Other Dementias

- **Vascular Dementia**
  - Higher percentage have psychotic sx. compared with AD (Ostling, 2011)
  - Delusions were nearly twice as common.
  - No association between degree of dementia severity and psychotic sx.
  - No difference between the quality of psychotic sx in AD and in VaD (LeRoi, 2003)

- **Psychotic sx are rare in FTD** (Mendez, 2008)
Depression with Psychosis

**Depression**
- ? Prior episodes/ Family history
- Unipolar (more common) vs. Bipolar
- Severe, potentially lethal → inpt
- Delusions of persecution or of having an incurable illness, guilt, focus on abdomen
- ECT first line treatment but patients tend to not like this idea
- Antidepressant +/- antipsychotic (usually)
References

- Boettger S. , Breitbart W. Phenomenolog of the Subtypes of Delirium: Phenomenological Differences between hyperactive and hypoactive delirium. Palliative and Supportive Care 2011: (9) 129-135.
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- Murray et al, Psychosis in Alzheimer’s Disease. Biological Psychiatry, Volume 75, Issue 7, 1 April 2014
References

Additional References


