PSYCHOSIS IN LATE LIFE

Beth LaBardi, MD

14 February 2023

DISCLOSURES

I have no financial conflicts of interest, and no commercial support has been received for this activity.

I will discuss off-label use antipsychotics for dementia-related psychosis given sparsity of FDA-approved medications for this indication. Available evidence for off-label use will be presented.

OBJECTIVES

1. Understand the heterogeneous causes of psychosis in late life
2. List important steps in the diagnostic evaluation of late life psychosis
3. Appreciate the role as well as potential limitations and risks of antipsychotic medications in older individuals

"PSYCHOSIS" DEFINITION:

- Not stated in the DSM-5 or the ICD classification systems
- "Psychotic features" include delusions, hallucinations, disorganized thinking, disorganized motor behavior, or negative symptoms
- Schizophrenia Spectrum and Other Psychotic Disorders (DSM 5) have these features as hallmarks

PSYCHOSIS IN LATE LIFE

Not uncommon

Varied etiologies

Develop due to the complex interaction between various biological, psychological, social, and environmental factors

More symptoms than actual disorders

Different clinical presentations

Associated with elevated morbidity and mortality

Talaslahti T, Alanen HM, Hakko H, et al. Patients with very-late-onset schizophrenia-like psychosis have higher mortality rates than elderly patients with earlier onset schizophrenia. *Int J Geriatr Psychiatry* 2015; 30: 453–459

PSYCHOTIC DISORDERS

PRIMARY

- Psychotic symptoms are part of the core symptoms of the disorder
  - Schizophrenia
  - Schizoaffective disorder
  - Schizophreniform disorder
  - Brief psychotic disorder
  - Delusional disorder
- Affective disorders
- Personality disorders

SECONDARY

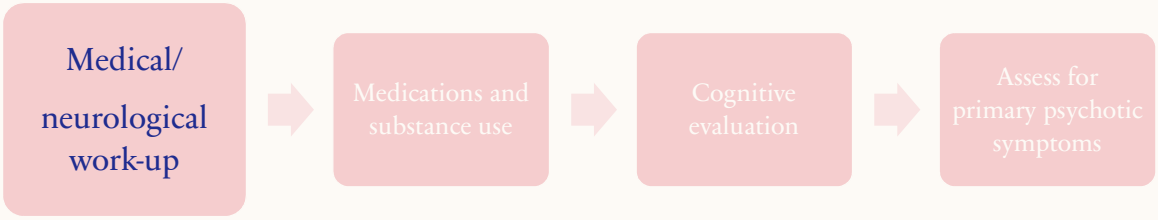
- Psychosis as a symptom of another disorder
  - Neurocognitive disorders
  - Delirium
  - Substance use
  - Medications
  - Other medical and neurological disorders (e.g., Parkinson's Disease)
- ~60% of cases of late life psychosis

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. 5th ed. Arlington, VA: American Psychiatric Publishing, Inc.)
Holroyd S, Laurie S. Correlates of psychotic symptoms among elderly outpatients. *Int J Geriatr Psychiatry* 1999; 14: 379–384

DIFFERENTIAL DIAGNOSIS AND WORK-UP

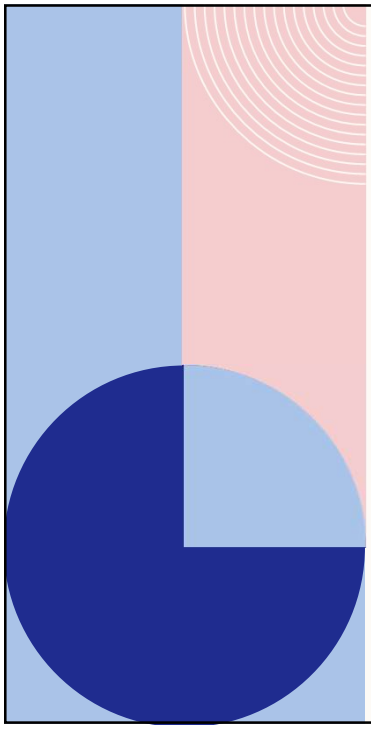
- Entertain a broad differential
- Until proven otherwise, assume new-onset psychotic symptoms in older adults are SECONDARY, so initial work-up should focus on these causes
- Individuals with secondary psychosis are:
  - More likely to have an atypical age of onset
  - More likely to have VH independent of AH
  - Less likely to have previous psychiatric history or family psychiatric history

DIFFERENTIAL DIAGNOSIS AND WORK-UP



DIFFERENTIAL DIAGNOSIS AND WORK-UP

- History
  - From patient and collateral sources
- Physical and neurological exam
- Labs
  - CBC, CMP, TSH, B12, Folate, RPR, HIV, UA, urine toxicology
- Neuroimaging



PSYCHOSIS IN DELIRIUM

- Acute onset
- Fluctuating course
- Unsystematized and fragmented delusions
- New cognitive deficits
  - Inattention, especially
- Prevalence of psychotic symptoms in delirium is ~42.7%
  - Visual hallucinations - 27%
  - Auditory hallucinations - 12.4%
  - Tactile hallucinations - 2.7%
  - Delusions - 25.6%

Webster R, Holroyd S. Prevalence of psychotic symptoms in delirium. *Psychosomatics* 2000; 41: 519–522

PSYCHOSIS IN PARKINSON'S DISEASE

- Hallucinations (especially VH) > delusions
- 10-40% of patients have at some point in illness
  - Risk factors include:
    - Higher dopaminergic medication load
    - Disease severity
    - Cognitive impairment
    - Poor visual acuity
    - Depression
- A poor prognostic indicator
  - More disabling than motor symptoms
  - Causes more caregiver distress
  - Threatens ability to remain at home

DIFFERENTIAL DIAGNOSIS AND WORK-UP

Medical/ neurological work-up → Medications and substance use → Cognitive evaluation → Assess for primary psychotic symptoms

Treat underlying organic causes

DIFFERENTIAL DIAGNOSIS AND WORK-UP

- Substance use history
- Thorough record of prescribed medications and OTCs
- Urine toxicology

MEDICATIONS AND SUBSTANCES

- ANY medication can cause late life psychosis
- Most commonly offending agents:
  - Anti-parkinsonian/dopaminergic medications
  - Anticholinergics
  - Sedative-hypnotics
  - Stimulants
- OTC agents
  - Antihistamines, sleep aides
  - Ask about those "PM" formulations!
- Substances
  - Ask! People continue use into late life.

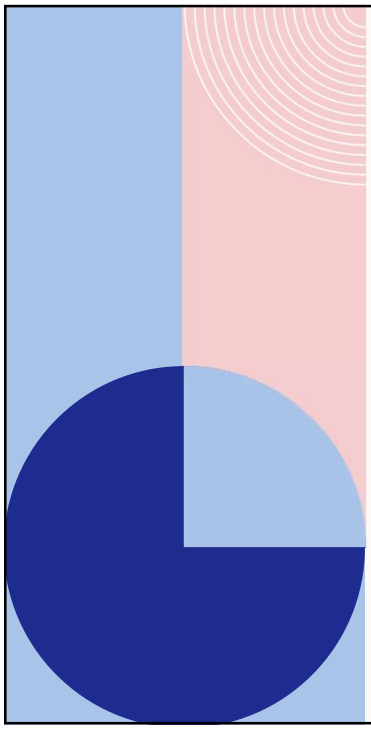
DIFFERENTIAL DIAGNOSIS AND WORK-UP

Medical/ neurological work-up → Medications and substance use → Cognitive evaluation → Assess for primary psychotic symptoms

Stop offending agents
Treat withdrawal and SUD

DIFFERENTIAL DIAGNOSIS AND WORK-UP

- Cognitive history
- Neuroimaging
- Neuropsychological testing



DEMENTIA-RELATED PSYCHOSIS

- THE MOST COMMON REASON FOR PSYCHOSIS IN LATE LIFE
- Overall pooled prevalence ~40%
- Convey greater cognitive and functional deficits
- Higher mortality

- Compared to schizophrenia:
  - More common in women
  - Less complex or bizarre delusions
    - Commonly persecutory or paranoid
  - More likely to experience misidentification
  - VH > AH
  - Unlikely to have thought-broadcasting or control of thought
  - Likely to eventually remit

DEMENTIA-RELATED PSYCHOSIS

ALZHEIMER'S DISEASE

- 41.1% prevalence
- Delusions > hallucinations

Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry* 2005; 162: 2022–2030

VASCULAR DEMENTIA

- ~15% prevalence
- Delusions > hallucinations

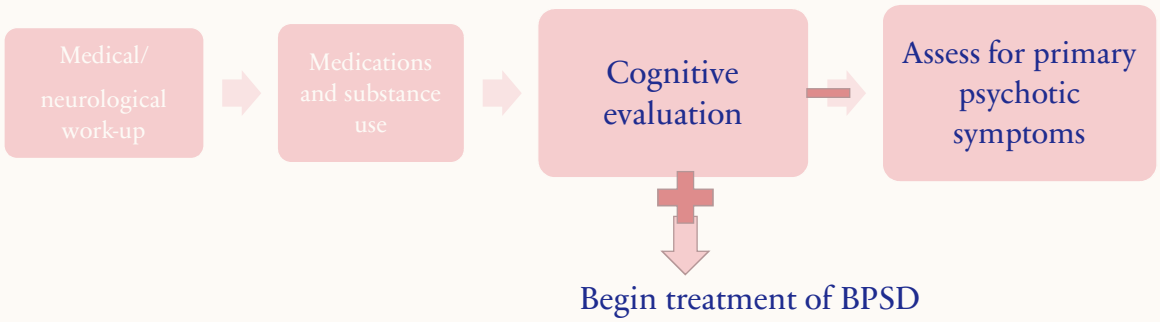
Leroi I, Voulgari A, Breitner JC, et al. The epidemiology of psychosis in dementia. *Am J Geriatr Psychiatry* 2003; 11: 83–91

DLB

- 78% prevalence of hallucinations
- 25% prevalence of delusions
- VH tend to be well-formed and detailed

Nagahama Y, Okina T, Suzuki N, et al. Classification of psychotic symptoms in dementia with Lewy bodies. *Am J Geriatr Psychiatry* 2007; 15: 961–967

DIFFERENTIAL DIAGNOSIS AND WORK-UP



DIFFERENTIAL DIAGNOSIS AND WORK-UP

- History of previous psychiatric illness
- Family psychiatric history
- Psychosocial assessment

PRIMARY PSYCHOTIC DISORDERS

- Schizophrenia - 0.1–0.5% prevalence in older adults
  - Lifetime prevalence of 1%
- Schizoaffective disorder
- Schizophreniform disorder (< 6 months)
- Brief psychotic disorder (1 day – 6 months)
- Delusional disorder

LATE LIFE SCHIZOPHRENIA

EARLY ONSET

- <40 years
- 75-80% of cases
- + Negative symptoms
- + Family history
- Heterogeneous course
  - "Disease of thirds"

LATE ONSET

- 40–60 years
- 20-25% of cases
- ♀ > ♂
- Less negative symptoms
- + Family history
- Sensory deficits, social isolation, premorbid paranoid/schizoid PD

VERY LATE ONSET SCHIZOPHRENIA-LIKE PSYCHOSIS (VLOSLP)

- >60 years
- ♀ >> ♂
- Rare negative symptoms
- Less family history

Ther Adv Psychopharmacol. 2019; 9: 2045125319882798. Psychotic disorders in late life: a narrative review Rajesh R. Tampi, Jaun Young, Rakin Hog, Kyle Resnick, and Deena J Tampi.
Harris MJ, Jeste DV. Late-onset schizophrenia: an overview. *Schizophrenia Bull* 1988; 14: 39
Stafford J, Howard R, Dalman C, et al. The incidence of nonaffective, nonorganic psychotic disorders in older people: a population-based cohort study of 3 million people in Sweden. *Schizophrenia Bull* 2019; 45: 1152–1160

SCHIZOAFFECTIVE DISORDER

- Psychotic symptoms in the absence of mood symptoms for at least 2 weeks
- Prevalence among adults ⩾60 years = 0.14%
- Depressive type > bipolar type
- ♀ > ♂, especially with later onset
- Compared to those with schizophrenia:
  - Have better community functioning
  - Poorer subjective physical and mental health
- Compared to younger adults with schizoaffective disorder:
  - Have greater severity of illness
  - Worse outcomes
    - Including greater treatment resistance and risk for suicide

Meesters PD, de Haan L, Comijs HC, et al. Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a Dutch catchment area. *Am J Geriatr Psychiatry* 2012; 20: 18–28
Post F. Schizo-affective symptomatology in late life. *Br J Psychiatry* 1971; 118: 437–445

DELUSIONAL DISORDERS

- Entrenched delusional systems, minimal hallucinations, lasting ⩾ 1 month
- Estimated prevalence among older adults = 0.03%
- More common in older adults
  - Average age of onset ~49 years old
- ♀ > ♂
- Limited knowledge about this disorder in older people

Gonzalez-Rodriguez A, Molina-Andreu O, Navarro V, et al. Delusional disorder: no gender differences in age at onset, suicidal ideation, or suicidal behavior. *Braz J Psychiatry* 2014; 36: 119–124
Maher B. Delusional thinking and cognitive disorder. *Integr Physiol Behav Sci* 2005; 40: 136–146

AFFECTIVE AND PERSONALITY DISORDERS

- Major Depressive Disorder
- Bipolar Disorder
- Paranoid Personality Disorder

MAJOR DEPRESSIVE DISORDER

- More likely to have psychotic symptoms in late life
  - Present in ~45% of older patients hospitalized for reasons related to depression
  - More common in those who are single, widowed, or living alone (sensory or social deprivation?)
- Delusions > hallucinations
  - Guilt - some relatively trivial episode from long ago currently viewed as a major problem (e.g., a one-time infidelity long since forgiven)
  - Somatic - fear of ongoing disease, often with somatic symptoms (often associated with the abdomen)
  - Nihilism
  - Persecution

Owoeye O, Kingston T, Scully PJ, et al. Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: comparisons with schizophrenia and bipolar I disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophr Bull* 2013; 39: 756–765

BIPOLAR DISORDER

- Rarely has onset in late life
- Psychotic symptoms are common in both affective phases
  - Mean frequency of psychotic features in bipolar disorder among the elderly that was pooled from a review of 5 studies was found to be 64%
  - Psychotic features more common with late onset

Gournellis R, Oulis P, Rizos E, et al. Clinical correlates of age of onset in psychotic depression. *Arch Gerontol Geriatr* 2011; 52: 94–98

PARANOID PERSONALITY DISORDER

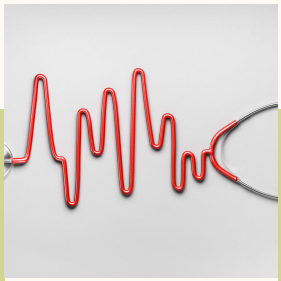
- ♂ > ♀
- Prevalence increases with age and medical comorbidities
- Distrustful of others
- Excessive trust in own knowledge/abilities
- Read hidden meanings into ordinary things
- Read hostile intentions into acts of others
- Appear cold and distant
- Quick to challenge loyalties of friends/family
- Shift blame to others
- Tend to carry long grudges

A CASE…

TREATMENT:
GENERAL PRINCIPLES

IS TREATMENT NECESSARY?

MEDICATION SELECTION AND INITIATION



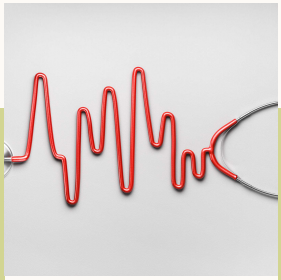
TITRATION AND MONITORING

REDUCTION AND DISCONTINUATION

TREATMENT:
GENERAL PRINCIPLES

IS TREATMENT NECESSARY?

MEDICATION SELECTION AND INITIATION



TITRATION AND MONITORING

REDUCTION AND DISCONTINUATION

IS TREATMENT NECESSARY?

FIRST, DO NO HARM

TREATMENT IN SCHIZOPHRENIA IMPROVES FUNCTIONING AND OUTCOMES

FDA BLACK BOX WARNING

PSYCHOSIS RESULTS IN HIGHER CAREGIVER DISTRESS AND CAN JEOPARDIZE PLACEMENT

FDA INDICATIONS:

SCHIZOPHRENIA, BIPOLAR DISORDER, MDD, PD PSYCHOSIS

BEERS CRITERIA RECOMMENDS AVOIDING USE FOR TREATMENT OF DEMENTIA AND DELIRIUM

PSYCHOSIS IS ASSOCIATED WITH POOR OUTCOMES

NO FDA INDICATION:

DEMENTIA WITH BPSD, INSOMNIA, ANXIETY

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-694

TREATMENT: GENERAL PRINCIPLES

IS TREATMENT NECESSARY?

MEDICATION SELECTION AND INITIATION

TITRATION AND MONITORING

REDUCTION AND DISCONTINUATION

MEDICATION SELECTION AND INITIATION

Limited studies of antipsychotics in older adults

Choose a medication with the most empirical evidence for the condition AND the best safety and tolerability

Educate patient and surrogate decision maker on adverse effects and risks

Document informed consent. Include risks, benefits, alternatives. Document your decision making clearly.

Start low (1/2 the starting dose for adults)

TABLE 2

ANTIPSYCHOTICS: SAFETY AND TOLERABILITY[1]

Item	Typical Neuroleptic	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
EPS	+ to +++	±	± to +++*	± to +*	±	± to +*	± to +
TD	+++	±	± to ++	± (?)	± (?)	± (?)	± (?)
Somnolence	± to +++	+++	±	++	++	±	±
Prolactin	+++	±	+++	±	±	±	±
Weight	± to ++	+++	+	+++	++	±	±
Dyslipidemia	± to +	+++	+	+++	++	±	±
DM	± to +	+++	+	+++	++	±	±
QTc	+	++	+	+	+	++	±
Orthostatic BP↓	± to +++	+++	++	+	++	±	±

*Dose-related.

Key: ±=none-to-minimal; +=mild; ++=moderate; +++=marked; ?=no data, compared to placebo rates.

EPS=extrapyramidal symptoms; TD=tardive dyskinesia; DM=diabetes mellitus; QTc=corrected Q-T interval; BP=blood pressure.

Glick ID, He X, Davis JM. *Primary Psychiatry.* Vol 13, No 12. 2006.

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SCHIZOPHRENIA

- 2018 systematic review and meta-analysis of antipsychotic drugs for elderly patients with schizophrenia:
  - 29 references - all RCTs
  - 1225 individuals
  - Mean age 57-73
  - Primary outcome of overall symptoms

Results:

- Paliperidone had fewer drop-outs due to inefficacy than placebo
- Olanzapine superior to haloperidol for overall symptoms and negative symptoms
- Risperidone and haloperidol increased prolactin more than olanzapine
- Olanzapine had less use of antiparkinsonian medication than haloperidol

Krause M, Huhn M, Schneider-Thoma J, Rothe P, Smith RC, Leucht S. Antipsychotic drugs for elderly patients with schizophrenia: A systmatic review and meta-analysis. Eur Neuropsychopharmacol. 2018 Dec;28(12):1360-1370

SCHIZOPHRENIA

- Dearth of high-quality pharmacotherapy studies in LOS and VLOSLP
  - Largest and best trials of risperidone and olanzapine
  - Smaller trials of newer agents
- Both 1st and 2nd generation antipsychotics are beneficial, but limited by adverse effects.
- Considerable pharmacological heterogeneity even within groups.
- Treatment of EOS in late-life using risperidone and olanzapine has Level 3 evidence
- Little evidence to support the use of clozapine in treatment-resistance geriatric patients due to its significant side effect profile
- Paliperidone also has some efficacy compared with placebo in the treatment of elderly patients with schizophrenia (Level 2 evidence)

Rothenberg KG, Boyd S, Sommerville R, et al. Clozapine in geriatric population-clinical indication and safety monitoring. *Am J Geriatr Psychiatry* 22: S73–S74
Mukku SSR, Sivakumar PT, Varghese M.Clozapine use in geriatric patients: challenges.*Asian J Psychiatr* 2018; 33: 63–67
Tzimos A, Samokhvalov V, Kramer M, et al. Safety and tolerability of oral paliperidone extended-release tablets in elderly patients with schizophrenia: a double-blind, placebo-controlled study with six-month open-label extension. *Am J Geriatr Psychiatry* 2008; 16: 31–43

DLB PSYCHOSIS

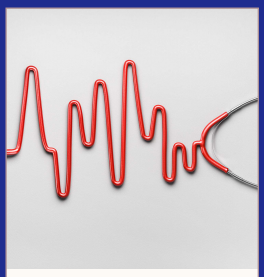
- **Donepezil** and **rivastigmine** can improve cognition, psychotic symptoms, and quality of life
- **Clozapine** has Level 2 evidence
  - Has greater serotonergic affinity and selective binding of D1 mesolimbic receptors while sparing striatal D2 receptors implicated in the deterioration of motor functions.
- One systematic review investigating the efficacy of **quetiapine** in patients with LBD found only one open-label trial that was able to report a significant reduction in psychotic symptoms
- **Pimavanserin** is a 5HT2A receptor inverse agonist, and has demonstrated efficacy in improving psychotic symptoms in Parkinson's disease, and in a group of mixed phenotype dementia-related psychosis

McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth Consensus Report of the DLB Consortium. *Neurology*. 2017;89(1):88–100
Tariot PN, Cummings JL, Soto-Martin ME, Ballard C, Erten-Lyons D, Sultzer DL, Devanand DP, Weintraub D, McEvoy B, Youakim JM, Stankovic S, Foff EP. Trial of Pimavanserin in Dementia-Related Psychosis. N Engl J Med. 2021 Jul 22;385(4):309-319
Factor SA, Friedman JH, Lannon MC; Parkinson Study Group. Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial. *Mov Disord* 2001; 16: 135–139
Desmarais P, Massoud F, Filion J, et al. Quetiapine for psychosis in Parkinson disease and neurodegenerative Parkinsonian disorders: a systematic review. *J Geriatr Psych Neurol* 2016; 29: 227-36

TREATMENT:
GENERAL PRINCIPLES

IS TREATMENT NECESSARY?

MEDICATION SELECTION AND INITIATION



TITRATION AND MONITORING

REDUCTION AND DISCONTINUATION

TITRATION AND MONITORING

- Go slow
- Aim for lowest effective dose
- Frequently assess for target symptoms and side effects
- AIMS, labs, weight, EKG as appropriate
- Avoid polypharmacy

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SCHIZOPHRENIA

- Lower dosing needed for LOS and VLOSLP
- EPS risk very high in VLOSLP
- Recommended dosing is based on expert consensus
  - Risperidone 1.25-3.5 mg/day as first-line
  - Alternatively, quetiapine 100–300 mg/day, olanzapine 7.5–15 mg/day, and aripiprazole 15–30 mg/day

Alexopoulos GS, Streim JE, Carpenter D.Commentary: expert consensus guidelines for using antipsychotic agents in older patients. *J Clin Psychiatry* 2004; 65: 100–102

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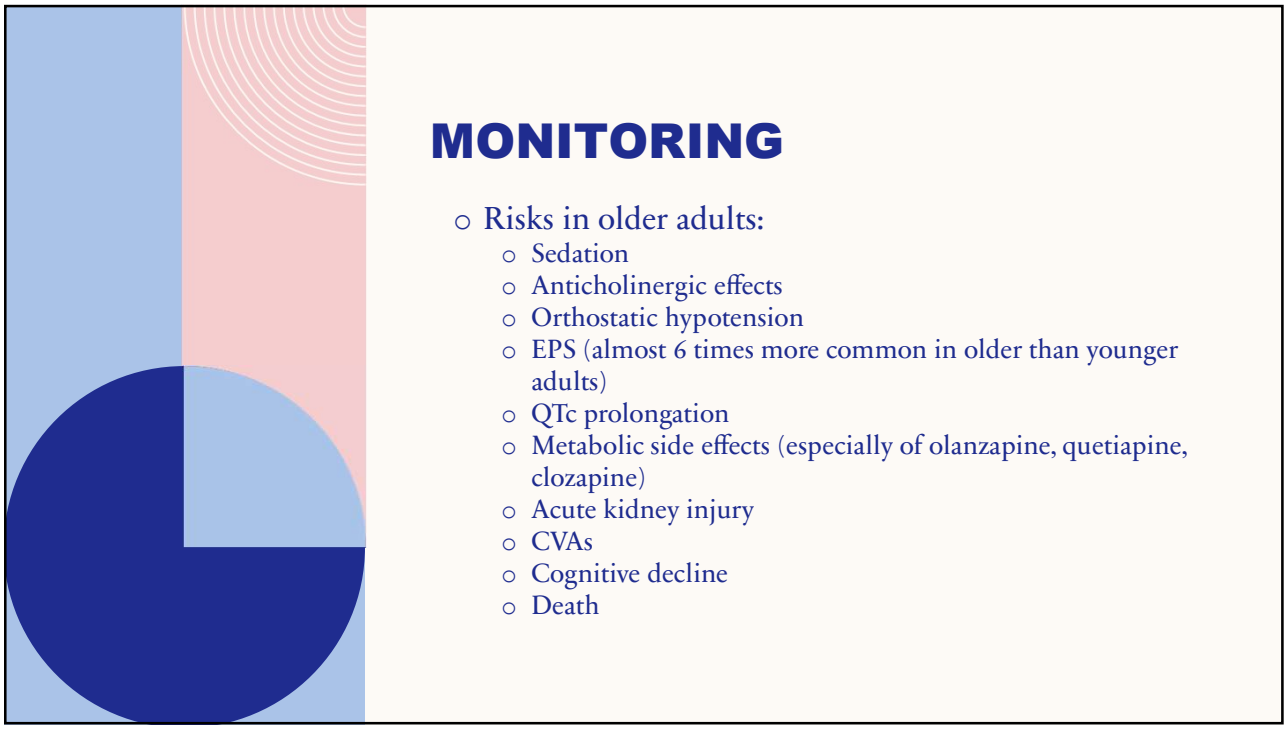
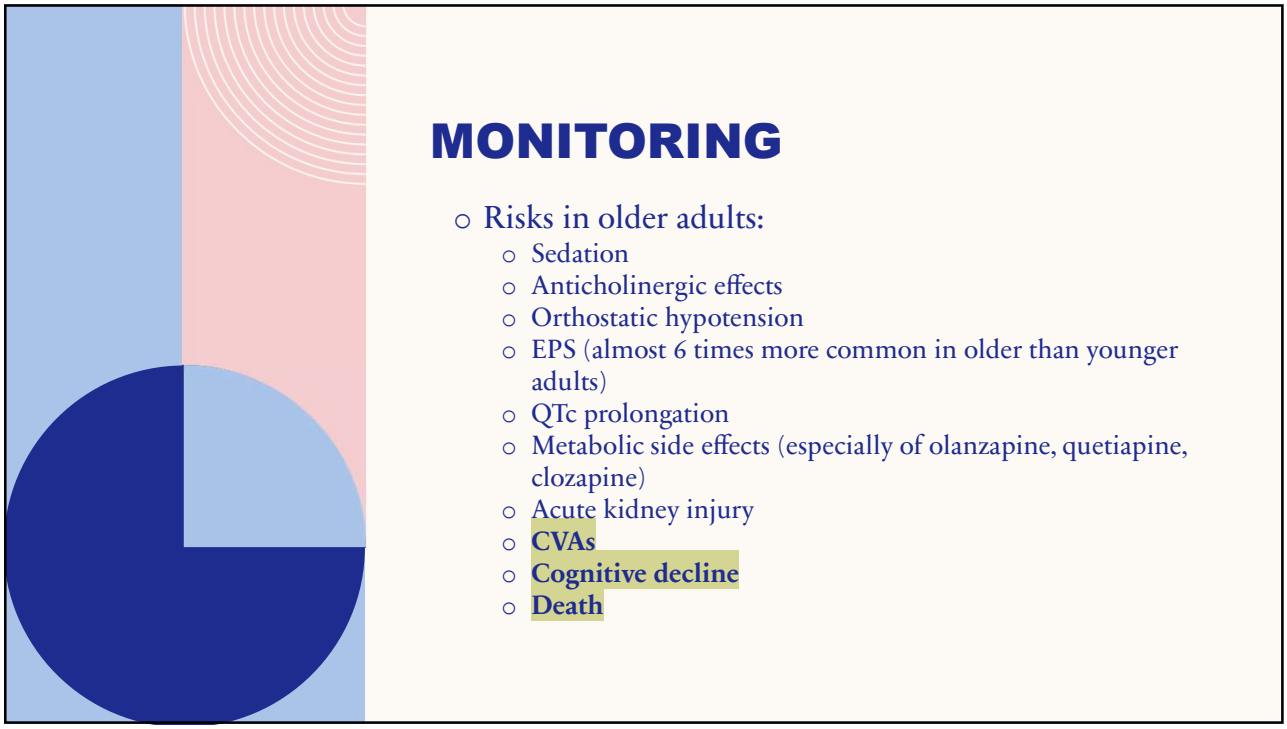
DLB PSYCHOSIS

- Caution with prescribing neuroleptics in patients with DLB!
- Risk of rigidity, neuroleptic malignant syndrome, and death as a consequence of the underlying disruption of dopaminergic neurotransmission
- Remember, clozapine has a significant side effect profile!
  - Orthostatic hypotension
  - Sedation
  - Agranulocytosis

Factor SA, Friedman JH, Lannon MC; Parkinson Study Group. Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial. *Mov Disord* 2001; 16: 135–139


MONITORING
Risks in older adults:
Sedation
Anticholinergic effects
Orthostatic hypotension
EPS (almost 6 times more common in older than younger adults)
QTc prolongation
Metabolic side effects (especially of olanzapine, quetiapine, clozapine)
Acute kidney injury
CVAs
Cognitive decline
Death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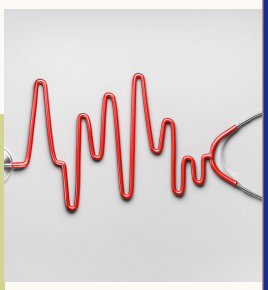
TREATMENT:
GENERAL PRINCIPLES

IS TREATMENT NECESSARY?

MEDICATION SELECTION AND INITIATION



TITRATION AND MONITORING

REDUCTION AND DISCONTINUATION

REDUCTION AND DISCONTINUATION

DURATION OF TREATMENT

- No clear data on how long to treat
  - After 3-6 months of stability?
- Taper, don't stop

GRADUAL DOSE REDUCTION (GDR)

- When used for dementia-related psychosis, consider dose reductions at least every 3 months
- "Lowest dose for the shortest duration"
- This is mandatory in long-term care settings

IF TREATMENT FAILS

- Reformulate the diagnosis, and medical/neuro/pharm etiologies
- Reassess previous med trials for adequate dose/duration
- Get consultation from a colleague

SCHIZOPHRENIA

- Data are limited regarding the discontinuation of antipsychotic medications in older adults diagnosed with chronic schizophrenia
- Attempt discontinuation of antipsychotics only in older patients who have not responded or those with long-standing clinical remission
- If discontinuation is not feasible, consider decreasing the dose of medications to the lowest effective dosage to minimize risk of adverse events

Takeuchi H, Suzuki T, Remington G, et al. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. *Schizophrenia Bull* 2013; 39: 993–998

ECT

- Safe in all ages, though fewer studies in the geriatric population
- Very effective for MDD or Bipolar disorder with psychosis
- Smaller body of literature for schizophrenia
- One selective review reports that prospective trials of ECT in psychotic elderly patients have indicated that bilateral ECT is a safe and effective treatment for older patients with schizophrenia
- Synergistic with concurrent antipsychotic therapy
- Best evidence for patients presenting with aggression, catatonia, and other cases that require rapid response such as acute suicidality or an acute onset of illness

Meyer JP, Swetter SK, Kellner CH. Electroconvulsive therapy in geriatric psychiatry: a selective review. *Psychiatr Clin North Am* 2018; 41: 79–93

PSYCHOSOCIAL TREATMENTS

- A number of programs (e.g., CBSST, FAST, HOPES) focusing on cognitive-behavioral interventions, social skills training, every day living skills, preventative health care, and vocational counseling/support have been conducted in middle-aged and older adults with benefit to psychotic symptoms, social functioning, and living skills.

Granholm E, McQuaid JR, McClure FS, et al: Randomized controlled trial of cognitive behavioral social skills training for older people with schizophrenia: 12-month follow-up. J Clin Psychiatry 68(5):730-737, 2007.
Patterson TL, Mausbach BT, McKibbin C, et al: Functional adaptation skills training (FAST): a randomized trial of a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. Schizophr Res 86(1-3):291-299, 2006.
Bartels, SJ Pratt, SI, Mueser KT, et al: Long-term outcomes of a randomized trial of integrated skills training and preventive healthcare for older adults with serious mental illness. Am J Geriatr Psychiatry 22(11):1251-1261, 2014.
Twamley EW, Padin DS, Bayne KS< et al: Work rehabilitation for middle-aged and older people with schizophrenia: a comparison of three approaches. J Nerv Ment Dis 193(9):596-601, 2005.

SUMMARY

- Psychosis in late life has variable presentations and etiologies
- Secondary causes are more common than primary psychotic disorders
- Work-up should be thorough to rule out the potential medical, neurological, medication or substance-related causes
- The most common cause of late life psychosis is dementia
- Early-onset schizophrenia has a considerably heterogeneous course into late life
- Late-onset schizophrenia and VLOSLP describe presentations with later life onset, and greater female predominance
- Older adults have a much higher risk of antipsychotic adverse effects, particularly EPS
- Antipsychotics have an FDA black box warning for their use in the setting of dementia
- There are (nearly) no FDA-approved treatments for psychosis related to dementia or delirium, but off-label use of medications along with non-pharmacological approaches may be appropriate on individual bases

THANK YOU!

Beth LaBardi, MD
Beth.LaBardi@va.gov