Aging with Serious Mental Illness

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Disclosures

- Dr. Russell Berg has no conflicts of interest to disclose
- Dr. Clayton English has no conflicts of interest to disclose

Presentation Agenda

- SMI and aging
- Silver tsunami of aging baby boomers
- Challenges managing SMI in aging patients
- Case 1: Chronic schizophrenia with dementia and progressive loss of ADLs
- Pharm update on treatment of schizophrenia in aging patients
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- Case 2: Major Depressive Disorder with psychotic features , failure to thrive
- Pharm update on treatment of severe depression with psychotic features in aging patients

- Case 3: Management of Bipolar 1 with severe treatment side effects
- Pharm update on management of movement side effects of antipsychotics

SMI in Aging Population

Serious Mental Illness = schizophrenia ,major depressive disorder, bipolar disord

- Most schizophrenia is diagnosed in early adulthood = 1% lifetime prevalence
  - > 25% of cases of schizophrenia diagnosed at age 40 or older = late onset schizophrenia

  10-15 year shorter life expectancy

  New psychotic sx may be sign of neurodegerative d/o

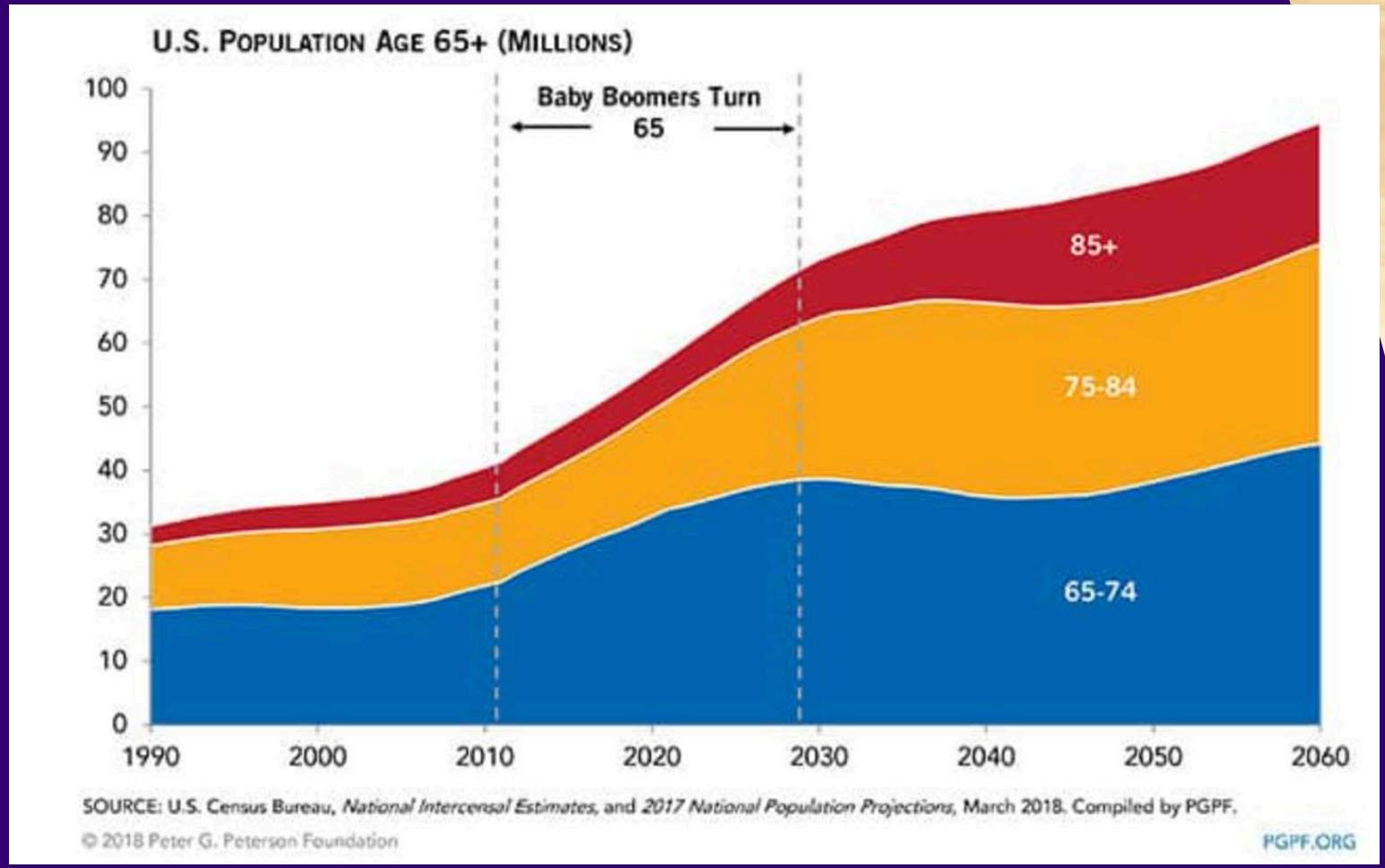
- Depression with psychotic features / psychotic depression –mean onset at 51 yrs
- lifetime prevalence of 0.35%
  - > 20-40% of patients hospitalized with depression have psychotic symptoms

- Bipolar d/o with psychotic features/ schizoaffective d/o
  - > 0.25-1% of elderly have bipolar d/o, 44% are diagnosed with late onset mania

Fischer, et al 2022 *Psychiatr Clin N Am*

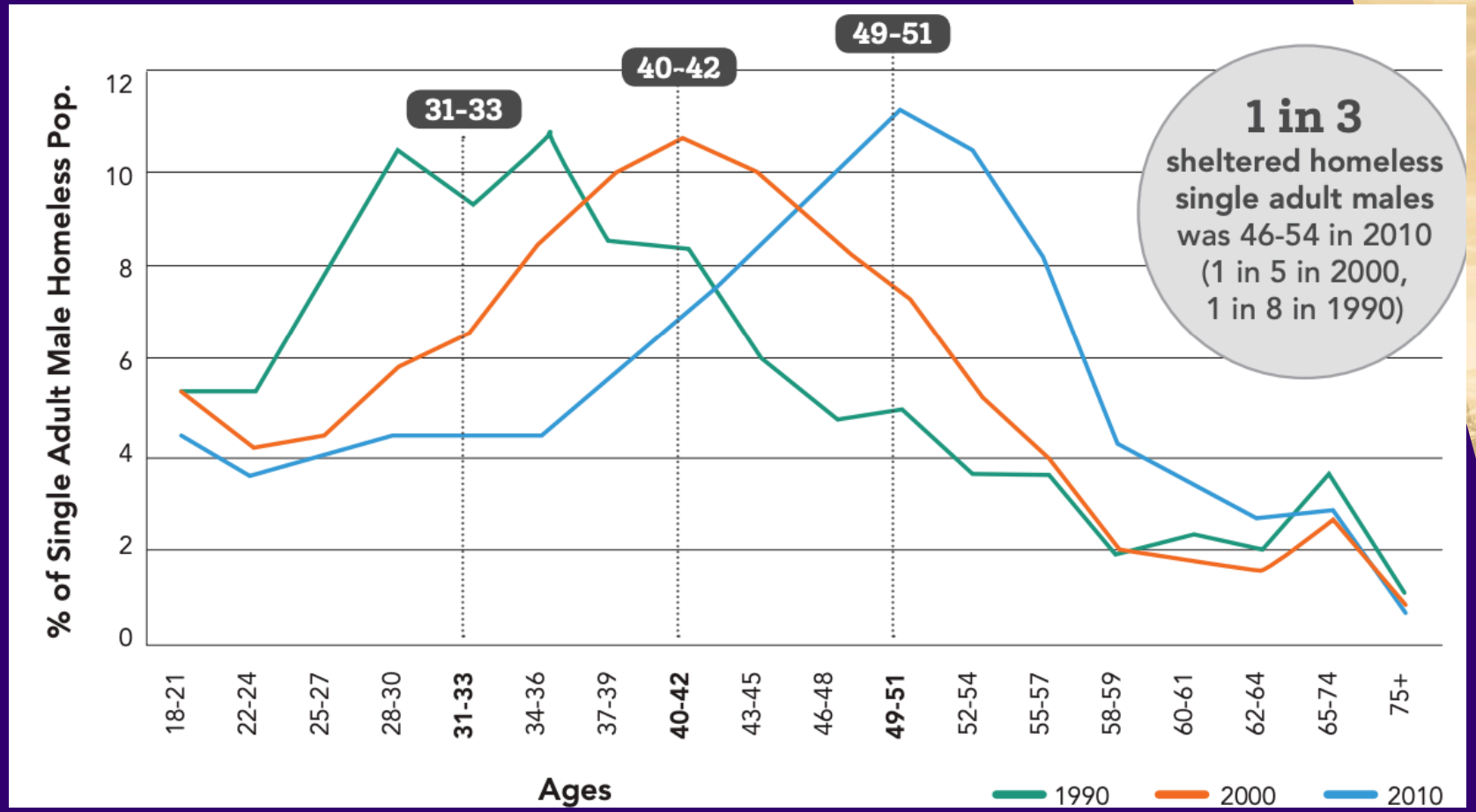
Silver Tsunami

- Aging baby boomers
- By 2030, those over age 65 with a major psychiatric disorder will be roughly equal to those aged 30 to 44



People experiencing homelessness are aging

- High proportion of homelessness and SMI co - morbidities
- Chronic homelessness disproportionately affects “late baby boomers” (b. 1955 -1965)



1. Brown et al., 2017; Brown, Kiely, Bharel, & Mitchell, 2012
2. Brown, et al, 2022
3. https://aisp.upenn.edu/wp-content/uploads/2019/01/Emerging-Crisis-of-Aged-Homelessness.pdf

Psychosis in Older Adults

- **Sufficient impairment of…**
  - > Thought processes
  - > Affective response
  - > Ability to recognize reality *(Loss of contact)*
  - > Ability to communicate and relate to others
- **Classic symptoms**
  - > Hallucinations, thought disorganization, and delusions *(fixed false beliefs)*

Disorders associated with Psychosis in Later Life
Schizophrenia (Early-Onset or Late-Onset)
Schizoaffective Disorder
Mood Disorders *(Major Depression with Psychotic Features or Bipolar Affective Disorder with Psychotic Features)*
Delusional Disorder
Neurodegenerative diseases *(Alzheimer's disease, Parkinson's disease, Lewy body dementia)*
Autoimmune disorders, CNS Infections, Cancer
Delirium
Stroke/Vascular dementia
Medication Induced Psychosis

The psychosis in these conditions often can cause deterioration of "normal" social function

Colijn MA, Nitta BH, Grossberg GT. Psychosis in Later Life: A Review and Update. *Harv Rev Psychiatry* 2015;23(5):354-367.

Special challenges to treating schizophrenia in elderly

- Older patients may have fewer and less severe positive symptoms (hallucinations, delusions)
- Negative symptoms tend to persist (withdrawal, isolation, catatonia)
- Psychotic symptoms with neurodegenerative disorders (AD, Lewy Body, PD)
- Rate of tardive dyskinesia >50% after 3 years of treatment w/ typical antipsychotics
- Atypical antipsychotics associated with elevated risk of mortality in those with dementia (1.6x risk of mortality), and increased risk of CVA

Folsom, et al. Schizophrenia in late life: emerging issues. Dialogues in Clin Neurosci, 2006 Mar; 8(1): 45-52

The Pharmacotherapy Balancing Act

Pharmacotherapy management is a balancing act that requires reconciliation of benefits/risks

Positives (+) associated with treatment:

- Psychosis is associated with poor outcomes, including suicide, thus treatment benefits often outweigh risks
- Treatment can make a difference including improving quality of life, decreasing caregiver burden, reduce risk of losing housing, and enhance functioning
- Likely prevents further progressive decline; however, this is more studied in younger populations

Negatives (-) associated with treatment:

- Antipsychotics lack the robust quality of studies performed in younger populations, thus empirical evidence often guides treatment selection in many cases
- Boxed warning of increased morbidity and mortality in patients with underlying dementia and antipsychotics are on the Beer's criteria list for select reasons
- Adverse effects and drug-drug interactions related to pharmacodynamic and pharmacokinetic changes often increase in older adults

Pharmacokinetic Changes in Older Adults

- Body Composition
  - > ⇩ lean body mass
  - > ⇩ serum albumin/⇧ α1-acid glycoprotein
  - > ⇩ total body water & ⇧ body fat
- Central Nervous System
  - > ⇩ Weight and volume of brain
  - > ⇩ p-glycoprotein transporter
- Renal System
  - > ⇩ renal blood flow & GFR
  - > ⇩ tubular secretion
  - > ⇩ renal mass
- Gastrointestinal System
  - > ⇩ gastrointestinal blood flow
  - > Slowed gastric emptying
  - > Slowed gastrointestinal transit
- Skin/Dermatological
  - > Loss of subcutaneous fat
  - > Thinning of dermis
- Hepatic System
  - > ⇩ mass & blood flow
  - > Δ's in oxidative metabolism (CYP isoenzymes)
- Pharmacodynamic Changes
  - – Change in receptor sensitivity and density including increased sensitivity to CNS medications

Polypharmacy

Overall goal is to reduce medication burden if possible given the risks, but there are some exceptions to keep in mind:

- Many conditions under the **SMI umbrella require polypharmacy** to adequately treat the condition:
  - Schizoaffective Disorder: Antipsychotic + Mood Stabilizer (in many cases)
  - Bipolar Affective Disorder: Mood Stabilizer +/- Antipsychotic
  - Depression with Psychotic Features: Antidepressant + Antipsychotic

- Adjuvant therapy is sometimes required given the treatment-emergent side effect, the patient history of response, or if there are a lack of other feasible options

- Augmentation (in cases of depression or refractory illness) might be preferred both by the patient and the treating clinician and is sometimes beneficial

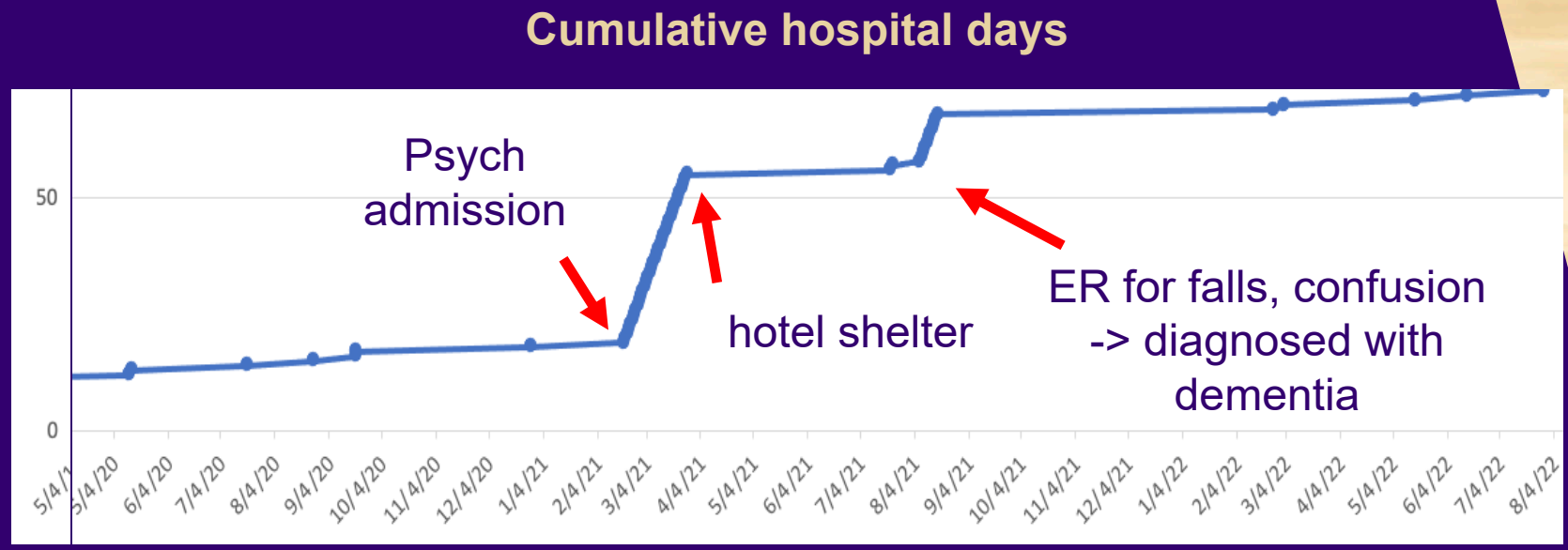
Case 1: Aging and Schizophrenia

Case 1: 78 year old man with psychosis and progressive dementia

- Released from a 30 yr prison sentence in 2013 at age 71
- Unstably housed 2013 -2021
- Admission 2021 for urinary retention and new psychosis, started on risperidone
- Discharged to hotel shelter April 2021

Case 1 : Psychosis and dementia

- Index admission March through April 2021 – diagnosed with psychosis
- Discharged to hotel shelter
- Medical encounters for back pain, urinary retention, UTIs, and progressive sx of confusion
- Positive sx of psychosis well controlled, he is socially isolated
- has not had contact with family for years

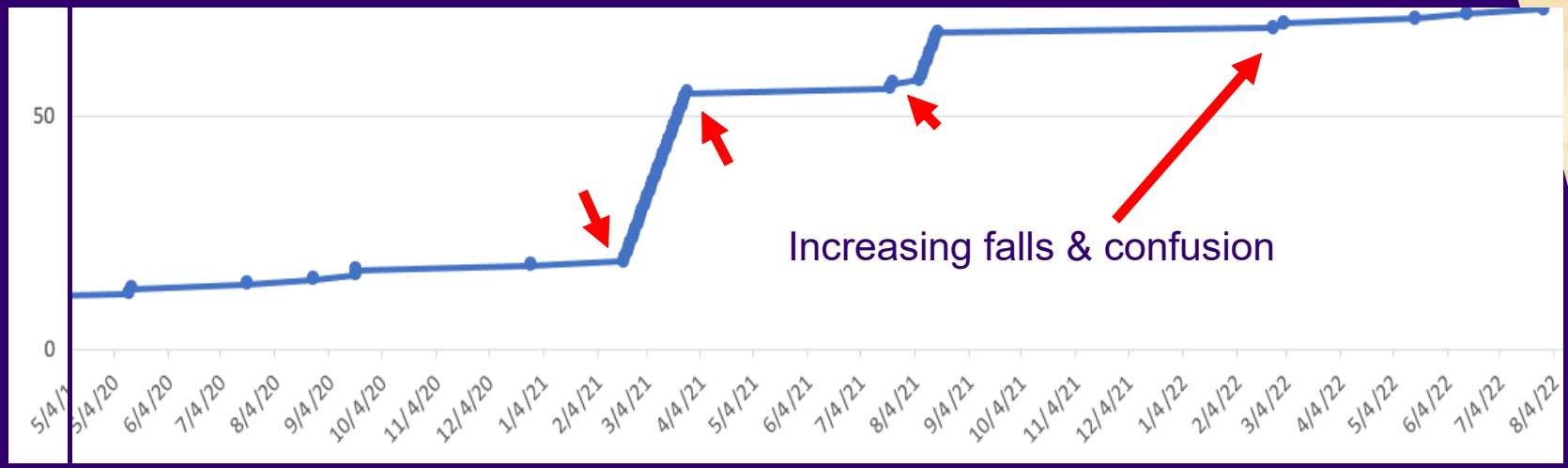


8/21 – admission for falls/confusion -> Medical workup negative for other causes, diagnosed with dementia, likely AD

Psychosis and progressive dementia

- Early 2022 - increasing falls and confusion - more ER visits.
- - 7/2022 - starts caregiver services at hotel shelter
- - wandering off and getting lost brought back by police after ER discharge - found at bus stop in the early morning in inappropriate clothing.
- - agrees to wear an apple air tag necklace

Cumulative hospital days

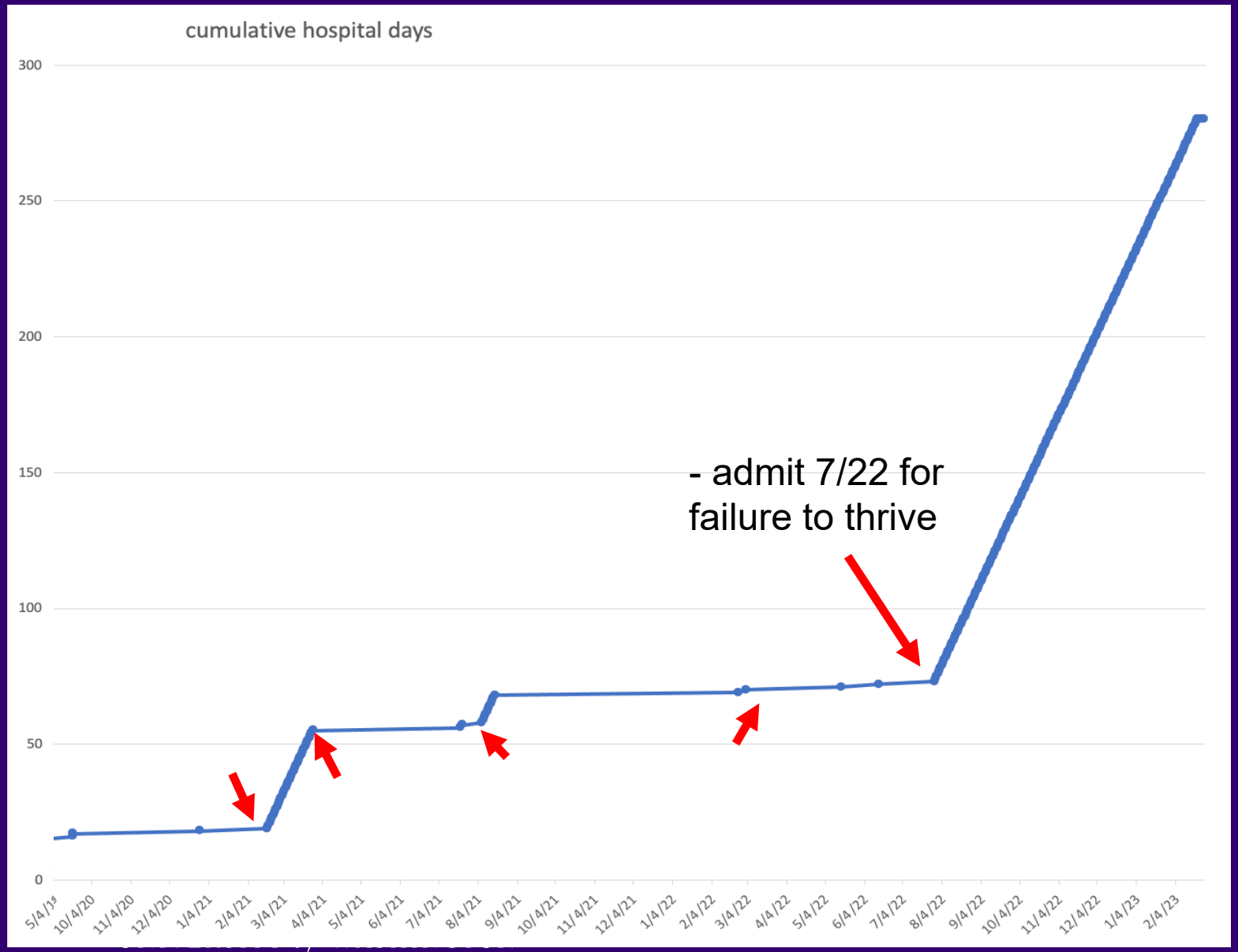


- late 7/2022 - wandering into other resident's rooms, at risk of assault, stops eating

-> sent to ER, admission for failure to thrive and grave disability

- medically barred from returning to hotel shelter - out of scope

Psychosis and progressive dementia



- 6 month admission for placement
- guardian appointed

-> discharged to memory care AFH.

- Died 6/2023 on Hospice care

- 208 hospital days in last year of life

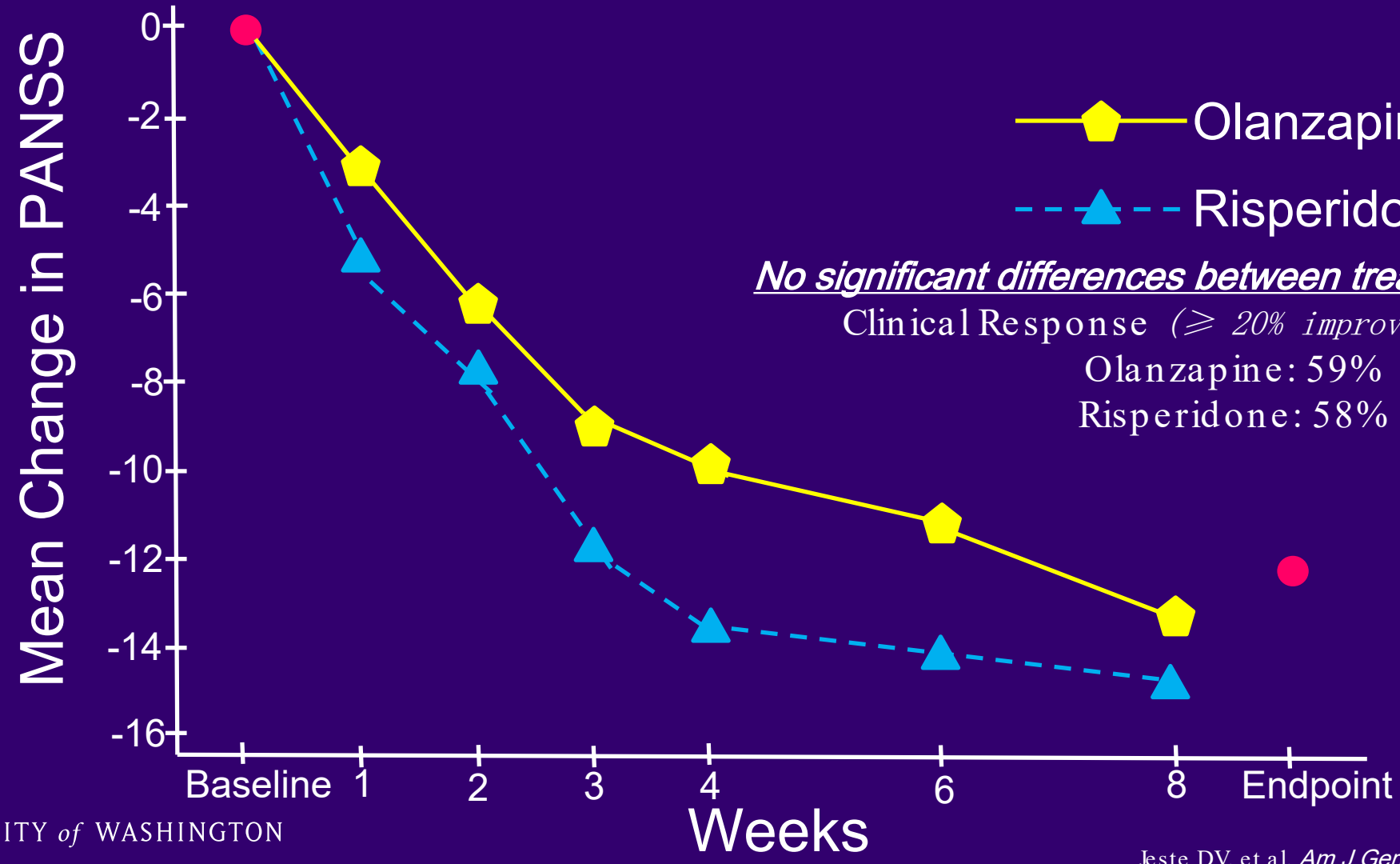
Pharmacotherapy of Late - Life Schizophrenia

- Atypical antipsychotics are primary treatment in late-life schizophrenia and have proved effective
  - > Most evidence supports use of risperidone and olanzapine
    - > Similar efficacy in large RCT
    - > Open-label trials have confirmed efficacy and tolerability
  - > Evidence supports clozapine for treatment-resistant patients, but additional studies are needed to replicate findings due to safety risk in older populations

- Prospective clinical trials with high quality methodology are lacking for other second generation antipsychtoics
  - > Lack of any data for newer medications (e.g., lurasidone, cariprazine)
- 1st generations have shown efficacy, but their use should be limited due to increase risk of tardive dyskinesia in older populations

Colijn MA, Nitta BH, Grossberg GT. Psychosis in Later Life: A Review and Update. *Harv Rev Psychiatry.*2015;23(5):354-367., Suzuki T, Remington G, Uchida H, Rajji TK, Graff Guerrero A, Mamo DC. Management of schizophrenia in late life with antipsychotic medications: a qualitative review. *Drugs Aging.*2011;28(12):961-980.

2nd Generation APs in Late - Life Schizophrenia



No significant differences between treatment groups

Clinical Response *(≥ 20% improvement in PANSS)*

Olanzapine: 59%

Risperidone: 58%

Jeste DV, et al. *Am J Geriatr Psychiatry* 2003;11(6):638-647.

Meta - Analysis: Antipsychotics in Late - Life Schizophrenia

- *Krause et al. (2018)*
- Included 18 unique randomized -controlled -trials with 1225 participants published from 1958 to 2009.
- No **major differences identified** of the effects of these drugs in the older adults
- Evidence based largely on small studies
  - > **Key findings:**
    - > Olanzapine was superior to haloperidol and had less need for antiparkinsonian medication
    - > Prolactin elevation higher in risperidone and haloperidol treatment groups vs. olanzapine
    - > No significant difference with paliperidone vs. placebo
      - > Efficacy measures did not show consistent statistical improvement between treatment groups

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

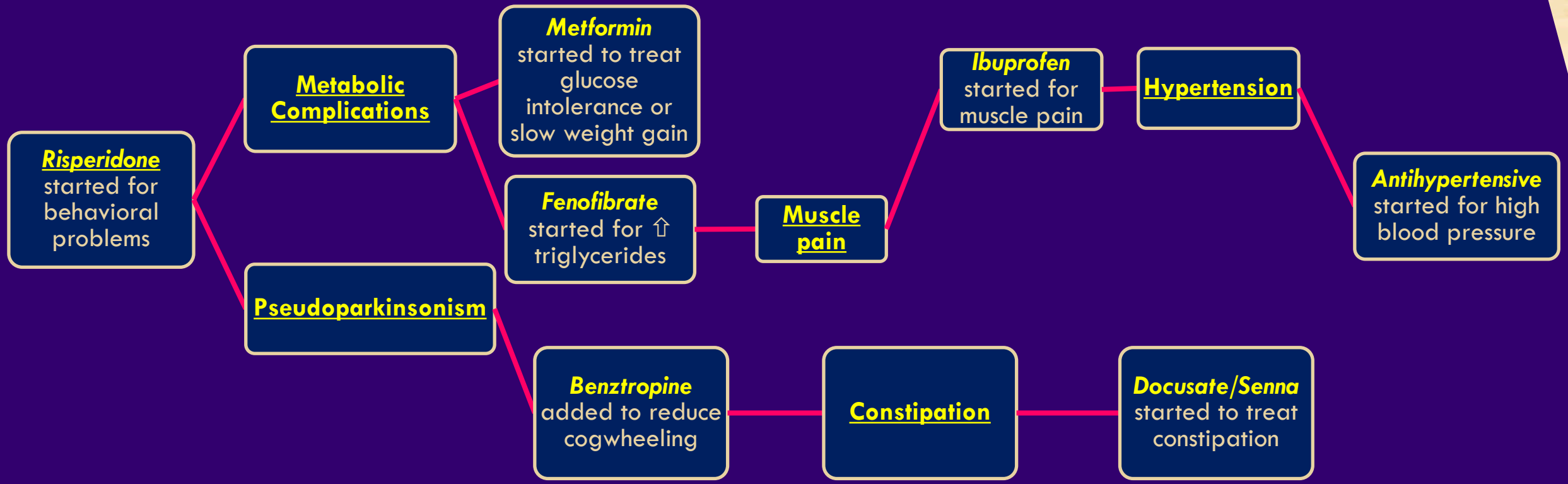
Antipsychotics in Late - Life

	Cardiovascular	Sedation	Anticholinergic	Miscellaneous
Aripiprazole/ Brexpiprazole	Little to none, mild QT prolongation	Low	Low	Akathisia, N/V (Brexpiprazole may have less EPS, activation risk vs. aripiprazole?)
Asenapine	QT prolongation	Moderate	None	Tongue numbing, allergic rxn., food restrictions
Cariprazine	Little to none, mild QT prolongation	Moderate	None	Akathisia, EPS
Clozapine	Orthostasis, tachycardia, myocarditis, qt prolongation	Very high	Very high	Neutropenia, seizures, sialorrhea, eosinophilia, high weight gain, metabolic concerns
Iloperidone	Orthostasis, qt prolongation	Low	None	Complex titration, less effective vs. typical APs
Lurasidone	Qt prolongation	Moderate	None	Absorption issues (350 calories required), Dose-related EPS-akathisia
Olanzapine	Qt prolongation, orthostasis	High	Moderate	High weight gain, metabolic concerns, ⇧ LFTs
Paliperidone	Qt prolongation	Low	None	Dose-related EPS, ⇧ Prolactin, OROS formulation
Quetiapine	Qt prolongation, orthostasis	High	Low-to-moderate	Cataracts (⇧ dose), weight gain, metabolic concerns
Risperidone	Orthostasis, tachycardia, qt prolongation, ⇧ risk of CVA in AD	Moderate	None	Dose-related EPS, Elevated prolactin, moderate weight gain
Ziprasidone	Qt prolongation (high)	Moderate	None	Absorption issues (500 calories required), N/V

Adapted from: Caulfield J. General Psychiatry. AACP Updates in Pharmacotherapy Review Course . AACP Publishing. Lenexa, KS. April 2015, Wells BG,, et al. Pharmacotherapy handbook . Ninth edition. ed. New York: McGraw -Hill; 2015.

Cascade Effect with Antipsychotics

- An adverse effect of an antipsychotic is interpreted as a new disease state
  - > Adverse effect is then treated with medication resulting in polypharmacy



Geller AI, Nopkhun W, Dows-Martinez MN, Strasser DC. Polypharmacy and the role of physical medicine and rehabilitation. *PM R*.2012;4(3):198-219.

Case 2: Major Depressive Disorder with Psychotic Features

Case 2: Major Depressive Disorder with Psychotic Features

- 75 yo female, recently lost spouse to long term chronic illness
- No surviving children, nearest relatives out of state.
- Concerned cousin flew to east coast to check on her and found her unkempt, hoarding
- Was able to fly back to live with relatives

Case 2: Major Depressive Disorder with Psychotic Features

- Here - appeared confused, talking to herself, vacant gaze, slow movements
- Taken to ER and admitted to psychiatry – psychosis with catatonia, cognitive impairment
- Some improvement with BZDs and olanzapine, still with persistent psychomotor slowing
- Inpatient, trialed on ECT with marked improvement psychomotor slowing and catatonia
- Discharged to Adult Family Home with ongoing maintenance ECT as outpatient

Drug - Drug Interactions in Older Adults

Atypical Antipsychotics	*CYP Metabolism*	*Typical Antipsychotics*	*CYP Metabolism*
Clozapine	1A2 (major), 3A4	**Chlorpromazine**	1A2 (minor), 2D6 (major), 3A4 (minor)
Risperidone	2D6	**Fluphenazine**	2D6 (major)
Olanzapine	1A2 (major);UDPG	**Haloperidol**	1A2 (minor), 2D6 (major), 3A4 (major)
Quetiapine	3A4	**Loxapine**	1A2 (major), 2D6, 3A4
Ziprasidone	Ald.Ox (major); 3A4	**Perphenazine**	2D6
Aripiprazole	2D6, 3A4	**Pimozide**	1A2 (minor), 3A4 (major)
Paliperidone	2D6, Renal	**Thioridazine**	2D6
Iloperidone	2D6, 3A4	**Thiothixene**	1A2
Asenapine	1A2, UGT1A4	**Trifluoperazine**	1A2
Lurasidone	3A4		
Brexpiprazole	2D6, 3A4		
Cariprazine	3A4		

PD interactions
QT prolongation
$M_{1,3}/\alpha_1/H_1$ effects

CYP1A2 inhibitors-fluvoxamine, primaquine, ciprofloxacin/***CYP1A2 inducers***-carbamazepine, cigarette smoking (specifically hydrocarbons combustion during smoking), omeprazole, rifampin, ritonavir
CYP2D6 inhibitors-amiodarone, bupropion (moderate), duloxetine (moderate), fluoxetine, paroxetine, ritonavir
CYP3A4 inhibitors-diltiazem (moderate), macrolide antibiotics, azole antifungals, nefazodone, protease inhibitors, verapamil/***CYP3A4 inducers***-carbamazepine, phenobarbital, phenytoin, primidone, rifampin

Older adults are at a higher risk for drug-interactions

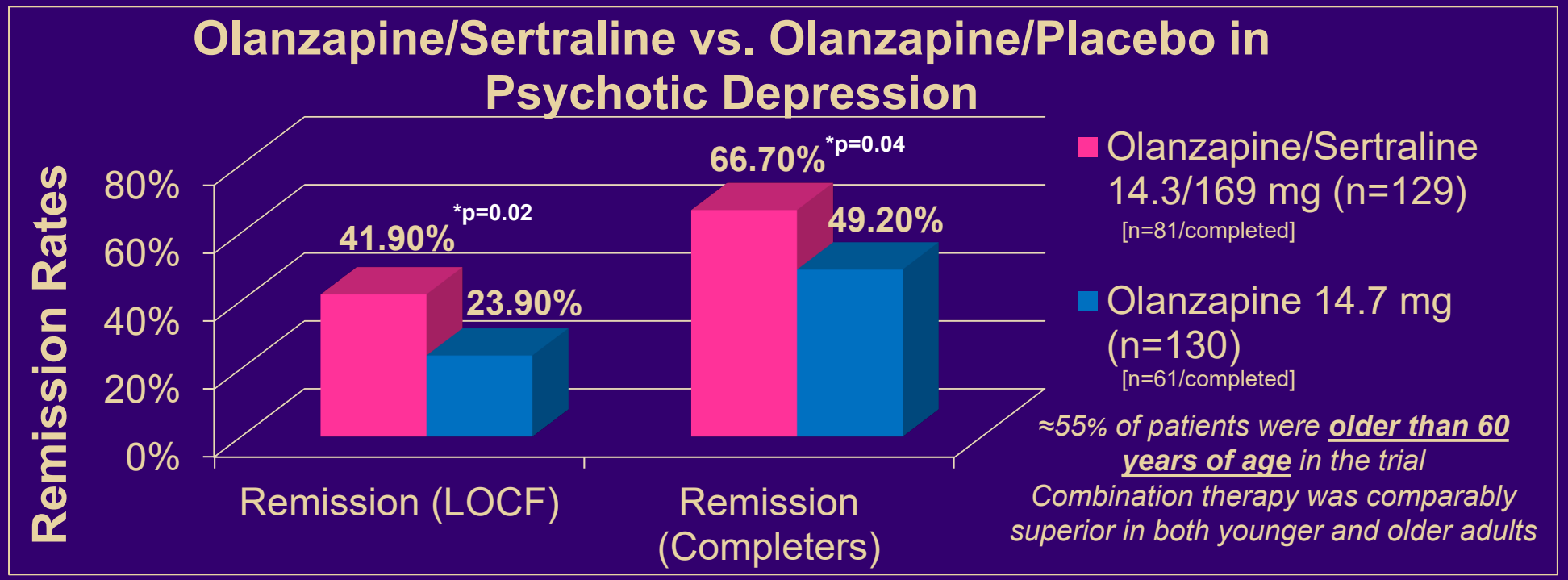
Source: Goldstone L. Schizophrenia & Other Psychotic Spectrum. CPNP 2016 Review Book. CPNP Publishing. Lincoln, NE. July 2016

Evidence Based Treatment Options - MDD with Psychosis

- No FDA approved therapy outside of amoxapine
- ECT should be considered for severe presentations if accessible or feasible
- Medication combinations with most evidence:
  - > Olanzapine + Sertraline
  - > Olanzapine + Fluoxetine
  - > Quetiapine + Venlafaxine
  - > Perphenazine + Amitriptyline
- Comparisons are unavailable to test relative safety and efficacy of individual antipsychotics and antidepressants
- Can consider other options if safety profile is not congruent with comorbidities
- Lithium augmentation for refractory cases, Positive case reports for clozapine

STOP - PD Clinical Trial

Meyers et al. 12 week RCT of Combination Antipsychotic/Antidepressant Treatment versus Antipsychotic Monotherapy for MDD w/Psychotic Features



Meyers BS, Flint AJ, Rothschild AJ, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry* 2009;66:838-47.

STOP - PD Adverse Effects by Age Group

	Total n (%)	Older (142) n (%)	Younger (117) n (%)	P-Value
Weight Gain	140 (54)	64 (45)	76 (65)	0.001
Somnolence/sedation	77 (30)	36 (25)	41 (35)	0.09
Gastrointestinal	64 (25)	33 (23)	31 (27)	0.55
Falls	36 (14)	23 (16)	13 (11)	0.24
Orthostatic Dizziness	33 (13)	21 (15)	12 (10)	0.28
Pedal edema/edema	24 (9.3)	19 (13)	5 (4.3)	0.01
Asthenia/Lassitude	24 (9.3)	13 (9.2)	11 (9.4)	0.95
Suicidal Ideation	21 (8.1)	10 (7)	11 (9.4)	0.49
Simpson Angus/EPS *(e.g., parkinsonism)*	2.1 (2.4)	2.9 (2.7)	1.2 (1.4)	<0.001
Akathisia	20 (7.7)	9 (6.3)	11 (9.4)	0.36
Tardive dyskinesia	22 (8.5)	12 (8.5)	10 (8.6)	0.98

Meyers BS, Flint AJ, Rothschild AJ, et al. A double-blind randomized controlled trial of olanzapine plus sertraline vs olanzapine plus placebo for psychotic depression: the study of pharmacotherapy of psychotic depression (STOP-PD). *Arch Gen Psychiatry* 2009;66:838-47.

Management of Metabolic Issues

Monitoring & Management

Parameter	Frequency of Monitoring
Personal/family history of metabolic disease, hypertension, or cardiovascular disease	Annually
Body weight and height	BMI at 4 weeks, 8, weeks, 12 weeks, and quarterly thereafter
Waist circumference	Annually
Blood Pressure	Every visit
FBG, HgbA1c	FBG or HgbA1c at 12 weeks and annually thereafter *[At-risk patients may require more frequent monitoring]*
Lipid panel	Lipid panel at 12 weeks and every 5 years *[At-risk patients may require more frequent monitoring]*

Management: Switch to another antipsychotic with a lower risk of metabolic adverse effects (unless treatment resistant illness), use behavioral interventions (e.g., nutrition/diet, exercise, health coaching), and/or treat metabolic disorders accordingly (i.e., pharmacotherapy for diabetes)

ECT Treatment Considerations

- Logistical challenges – 3x weeky treatment, limited availability. Continuation and maintenance ECT. Require escort home, advised to avoid making important personal or work decisions while receiving treatment

- Cognitive side effects are common but tend to improve by 2 weeks post treatment

- Contraindications
  - Cardiovascular disease, pulmonary disease, pacemakers

Case 3: Antipsychotic induced movement disorder

Case 3: Antipsychotic induced movement disorder

- 60 yo man, accomplished member of criminal justice system

- he and his family received death threats -> moved with wife to live with adult daughter in the US.

Case 3: Antipsychotic induced movement disorder

- prior diagnosis of depression, prior suicide attempt

- Shortly after moving to USA, hospitalized after choking his daughter in a parking lot

-> Inpatient psychiatry admission, diagnosed with bipolar disorder 1
    - stabilized well on lithium

- He still felt like he had good years in him (early 60s) and wanted to learn English, get involved in his community.

- volunteered to help people fill out residency, asylum and citizenship paperwork.

Case 3: Antipsychotic induced movement disorder

-Side effects of treatment - lithium therapy led

-> hypothyroidism, tremor, nephrogenic diabetes insipidus and urinary incontinence

-> titrated off lithium to carbamazepine, but had persistent hypomanic episodes

➔ Therapy changed to Depakote + olanzapine

➔ Developed Parkinsonism with bradykinesia, cogwheeling rigidity, mask facies, -> pramipexole added to manage this s/e with limited benefit

➔ Admission for falls, rehab SNF stay now home again and continues to occasionally fall

Case 3: Antipsychotic induced movement disorder

- Titrate to a different antipsychotic/ mood stabilizer with fewer movement s/e and risk manic episode ?

- Add additional medications to manage side effects?

- Go back to lithium and accept that side effect profile?

- Accept as unavoidable side effect for some patients?

Acute Movement Disorders in Older Adults

EPS	Time to Onset	Risk Factors in Older Adults	Dosing Strategy	Switch Strategy	Medication
Akathisia	Days to weeks after initiation or dose increase	Increased sensitivity to dopamine blockade; Polypharmacy (SSRI/SNRI use); Age-related changes in drug metabolism	Reduce antipsychotic dose if possible	Switch to lower-risk SGA (e.g., quetiapine)	Consider lipophilic beta-blockers (e.g., propranolol)
Dystonia	Hours to days after initiation or dose increase	Less common in older adults; Higher risk with high-potency FGAs; Neurological comorbidities may increase susceptibility	Discontinue	Switch to an SGA with lower dystonia risk (e.g., most –pine type medications)	Use anticholinergics (e.g., benztropine) or benzodiazepines for acute relief
Pseudoparkinsonism	Weeks to months after initiation	Age-related dopamine depletion; Increased risk with high-potency FGAs; Pre-existing parkinsonian features/movement disorders	Reduce dose if possible	Switch to SGA with lower EPS risk (e.g., most–pine type medications)	Consider cautious use of anticholinergics (e.g., benztropine) if absolutely needed

Tardive Dyskinesia and Older Adults

EPS	Time to Onset	Risk Factors in Older Adults	Dosing Strategy	Switch Strategy	Medication
Tardive Dyskinesia (Delayed)	Months to years after chronic use	Higher risk in women; higher cumulative antipsychotic exposure; Increased dopamine receptor upregulation; Age-related vulnerability to motor side effects	Gradual dose reduction when possible to mitigate worsening; avoid abrupt discontinuation	Can consider switch to clozapine under certain circumstances or possibly another –pine medication	VMAT2 inhibitors (e.g., valbenazine, deutetrabenazine); Avoid anticholinergics as they may worsen symptoms

- Valbenazine and deutetrabenzaine both have shown clinical improvements in older adults with TD
- Be mindful of QT prolongation, worsening of depression, or inducing acute movement disorders

Key Takeaways and Summary

- The older adult population presents unique challenges in treating serious mental illness (SMI), especially with the increasing prevalence of co -occurring chronic conditions and concomitant polypharmacy
- Pharmacologic treatment in aging patients requires careful consideration of drug efficacy and side effects, particularly for schizophrenia, depression with psychotic features, and bipolar disorder
- Movement -related side effects from antipsychotics are a significant concern in older adults, requiring tailored management strategies to reduce discomfort and improve quality of life
- Multidisciplinary approaches and individualized care plans are essential for optimizing treatment outcomes and addressing the complex needs of aging patients with SMI

Questions