Antipsychotic Medications in Geriatric Patients: Efficacy, Safety and Concerns

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Objectives

- Discuss the evidence related to the rationale for use of atypical antipsychotics in the elderly
- Discuss the risks associated with the use of atypical antipsychotics in the elderly
- Review the pros and cons of the available atypical antipsychotic medications

Background

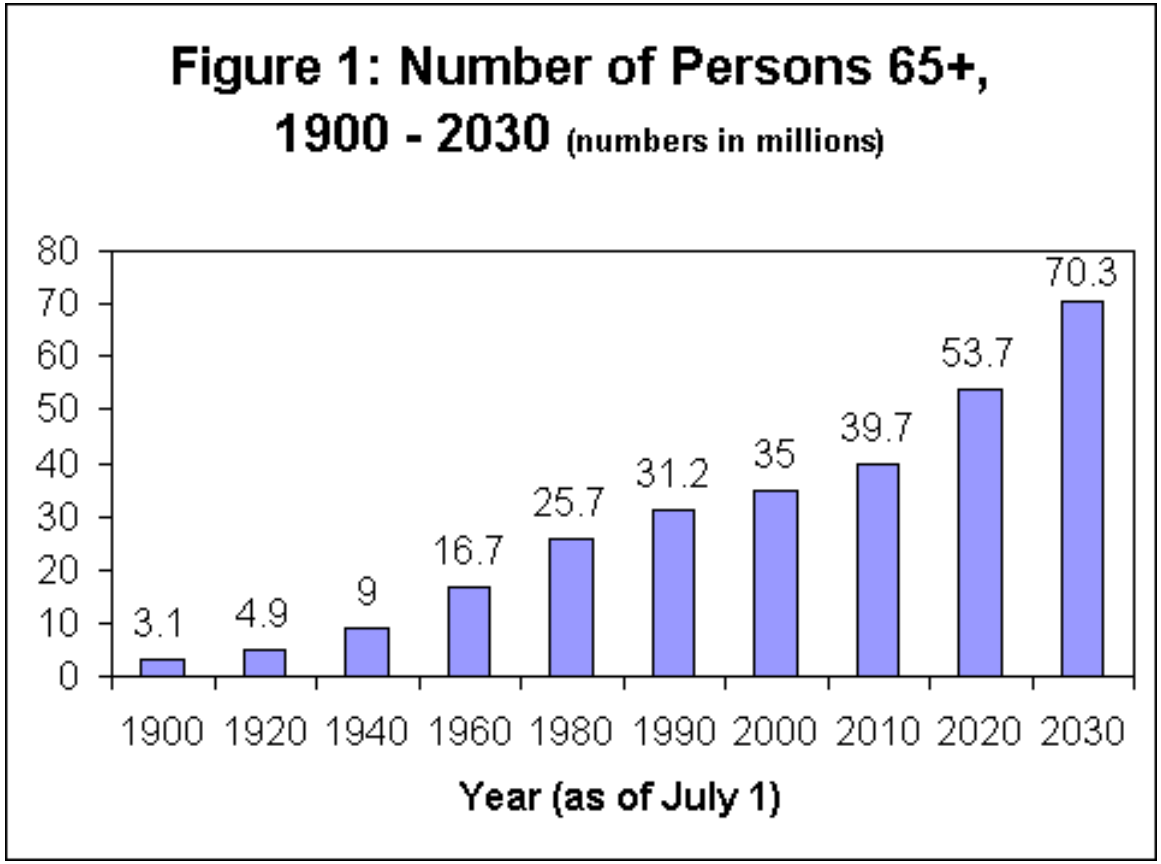


Figure 1: Number of Persons 65+, 1900 - 2030 (numbers in millions)
80
70
60
50
40
30
20
10
0
3.1
4.9
9
16.7
25.7
31.2
35
39.7
53.7
70.3
1900 1920 1940 1960 1980 1990 2000 2010 2020 2030
Year (as of July 1)

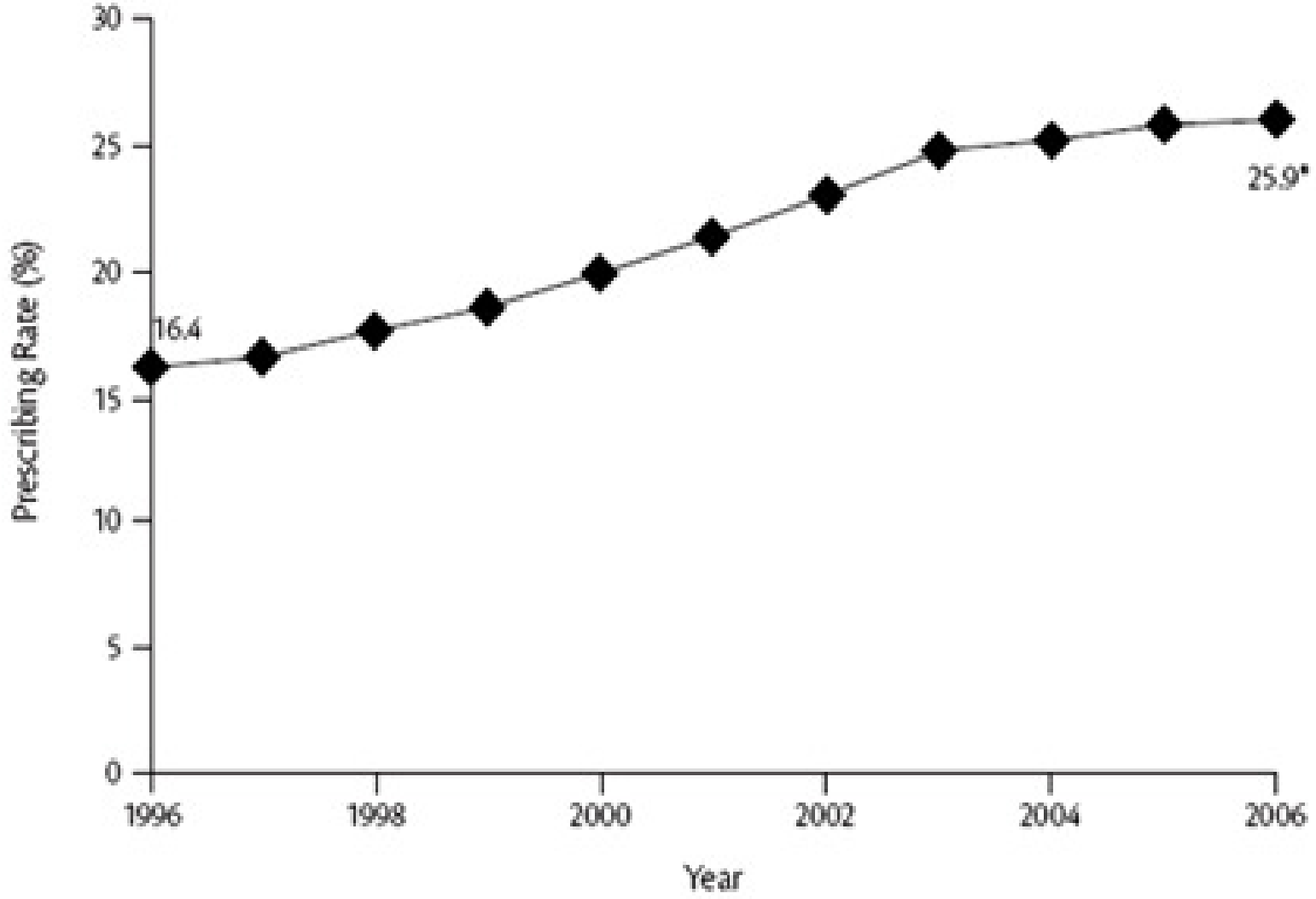
Background

- The Oldest Old
  - Fasting growing population : 85+
  - 38% rise from 1996 – 2010
  - Results in increasing care in long term care facility which may result in behavior issues

Facts on Antipsychotic Use in Older Adults

- Half of nursing home residents have dementia
- 25% of nursing home residents receive antipsychotic medications
- No antipsychotic is approved for treatment of dementia

Antipsychotic Prescribing in US Nursing Homes Between 1996 and 2006, Based on Medicare and Medicaid Data



Castle NG, et al. *Am J Geriatr Pharmacother.* 2009;7:143.

Case

- Dale an 85 yo male has been living at home with his wife for the past 55 years.
- Dale was diagnosed with dementia 5 years ago and his wife currently takes care of him
- Dale has always stated that he does not want to live in a nursing home
- Dale's wife was recently diagnosed with Leukemia and is having trouble taking care of him
- Dale has been increasingly more hostile and aggressive towards her
- His wife realizes it is time for a nursing home but hopes it is just for a short time while she is treated for her leukemia

Case – Nursing Home Admission

- During the admission process, Dale becomes very hostile towards his wife and the nursing home staff
- Dale threatens to kill his wife for putting him there and attempts to swing a few punches at the nursing staff

Clinical Question

- Since Dale is showing some agitation and aggression towards nursing staff and wife, should we administer some PRN antipsychotics?

  € YES

  € NO

Behavioral and Psychological Symptoms of Dementia (BPSD)

BPSD Symptoms

- Behavioral
  - Physical aggression
  - Wandering
  - Restlessness
  - Agitation
  - Culturally inappropriate behavior and disinhibition
  - Pacing
  - Screaming
  - Crying
  - Cursing
  - Lack of drive
  - Repetitive questioning
  - Shadowing
- Psychological
  - Delusions
  - Hallucinations
  - Depression
  - Sleeplessness
  - Anxiety
  - Misidentifications

BPSD Educational Pack. International Psychogeriatric Association. 1998

Agitation

- What is agitation?
  - Very non-specific term
  - Many definitions
    1. Violent motion or stirring
    2. Discussion meant to stir people up
    3. Extreme emotional disturbances
- Try to use more specific terms
  - Restlessness, aggression, or socially inappropriate behavior

Common Causes of BPSD in Older Adults

- Environmental triggers of BPSD
  - Anger or fear
  - Frustration (e.g., task completion)
  - Anxiety about being bathed, dressed, or toileted
  - Response to new surroundings
  - Response to recent stressors
  - Noise; change in routine; lack of structure throughout day
  - Overstimulation/under stimulation

Common Causes of BPSD in Older Adults

- Delirium
- Side effects of medications
- Pain syndromes
- Infection
- Fecal impaction
- Dehydration
- Patient cannot verbalize
- Hypoxemia or confusion (e.g., CHF, COPD)

General Principles of BPSD

- No specific symptom for a particular dementia.
- Social withdrawal, depression and paranoia usually occur in the early stages of dementia
- Symptoms vary from individual to individual.
- Intensity of psychiatric symptoms wax and wane over time.
- Symptoms may have a diurnal variation (e.g. occur at sundown)
- Psychiatric symptoms may improve over time.

NO CURE

Non-drug Approaches

AGITATION/ANGER

- Provide quite time and a calming environments
- Ensure low vision/hearing are not the problem
- Have a daily routine
- Provide distraction with a favorite food or activity
- Avoid increasing agitation when communicating
  - Don't ask questions that rely on memory
  - Speak slowly, clearly and simply

HALLUCINATIONS/DELUSIONS

- If not distressing - Ignore
- Don't disagree with a false idea directly
- Don't argue with a suspicious person
- Provide sufficient lighting at night to avoid hallucination that are triggered by shadows

Dale- follow-up

- Dale was moved to a quieter room until the admission process was done
- Dale remained agitated but no medications were given.
- Dale was more cooperative with staff and physicians the following day

Dale –Continued

- Dale has been in the nursing home for over 3 months and non-pharmacological techniques have been helping Dale, however over the last months his symptoms are starting to worsen and has been in several altercations with the nursing staff (broke a nurses arm)
- The physician thinks it is time to start medication therapy

Use of Antipsychotics in Older Adults

Uses of Antipsychotics in Long Term Care Facilities

- Treatment of psychotics disorders
- Treatment of psychotic symptoms
  - Delusions
  - Hallucinations
  - Often associated with Alzheimer's disease or delirium
- Treatment of behavioral and psychological symptoms (BPSD)

Potential Complications of Prescribing Antipsychotic Medication in Dementia

- Accelerated cognitive decline
- Mortality
- Metabolic syndrome
- EPS
- Stroke
- Falls

Antipsychotics Indication

FDA indications

- Schizophrenia , Bipolar Disorder
- Irritability associated with autism disorder (risperidone, aripiprazole)
- Major Depression (aripiprazole, quetiapine)

Off-label uses

- Sleep
- Behavioral
- Anxiety, PTSD, OCD

When is it Appropriate to use Antipsychotics in Older Adults

- After non-drug behavioral management strategies have been unsuccessful
- If behaviors causes danger or severe distress to person or other

Appropriate Target Symptoms to use Antipsychotics

- Aggressive behavior
- Hallucination
- Delusions

Inappropriate Treatment Targets for Antipsychotics

- Wander
- Unsociability
- Poor self-care
- Restlessness
- Nervousness
- Fidgeting
- Mild Anxiety
- Impaired memory
- Uncooperativeness
- Inattention or indifference to surrounds
- Verbal expressions or behaviors

Antipsychotic Medications

TYPICAL ANTIPSYCHOTICS
(A.K.A. CONVENTIONAL OR 1ST GENERATION)

- chlorpromazine (Thorazine®)
- thioridazine (Mellaril®)
- mesoridazine (Serentil®)
- loxapine (Loxitane®)
- molindone (Moban®)
- perphenazine (Trilafon®)
- trifluoperazine (Stelazine®)
- thiothixene (Navane®)
- fluphenazine (Prolixin®)
- **haloperidol (Haldol®)**

ATYPICAL ANTIPSYCHOTICS
(A.K.A. 2ND GENERATION)

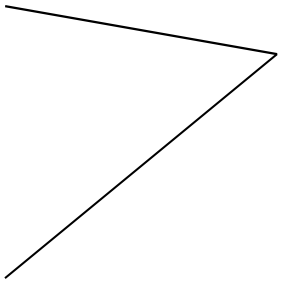
- Clozapine (Clozaril®)
- Olanzapine (Zyprexa®)
- Risperidone (Risperdal®)
- Paliperidone (Invega®)
- Quetiapine (Seroquel®)
- Ziprasidone (Geodon®)
- Asenapine (Saphris®)
- Iloperidone (Fanapt®)
- Lurasidone (Latuda®)
- Aripiprazole (Abilify®)

Side Effects of Antipsychotic

- Drowsiness
  - Some are more than other
  - Usually resolves in a few week
- Anticholinergic Side Effects
  - Dry Mouth
  - Constipation
  - Urinary retention
  - Blurred vision
  - Increase heart rate
  - Decreased sweating

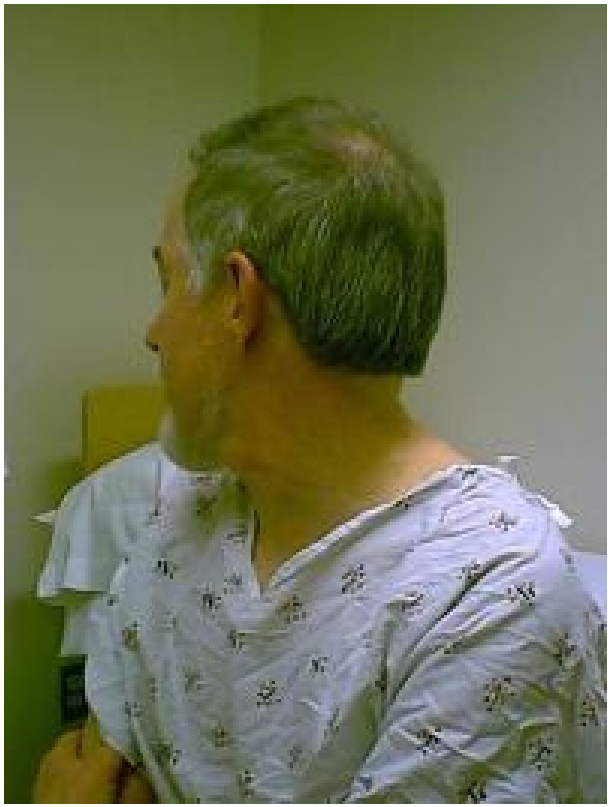
Side Effects of Antipsychotic Treatment

- Cardiovascular side effects
  - Postural hypotension/ Arrhythmias
- Increase Prolactin
  - Galactorrhea, amenorrhea
- Extrapyramidal Side Effects (EPS)
  - Dystonias
  - Pseudoparkinsonism
  - Tardive Dyskinesias
  - Akathisias



Most Commonly seen with the typical or older agents

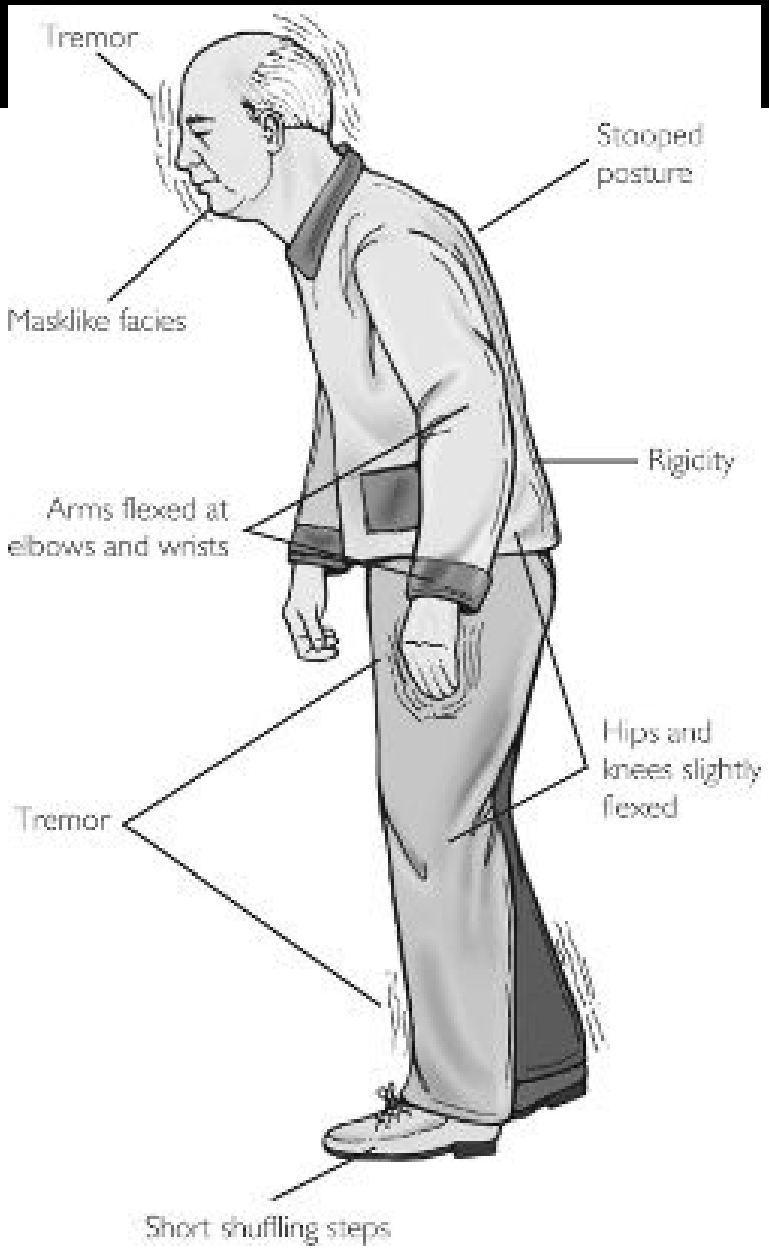
Dystonia



Treatment

Benztropine (Cogentin) or Diphenhydramine (Benadryl)

Pseudoparkinsonism



Treatment

Benztropine (Cogentin)
or
Diphenhydramine (Benadryl)

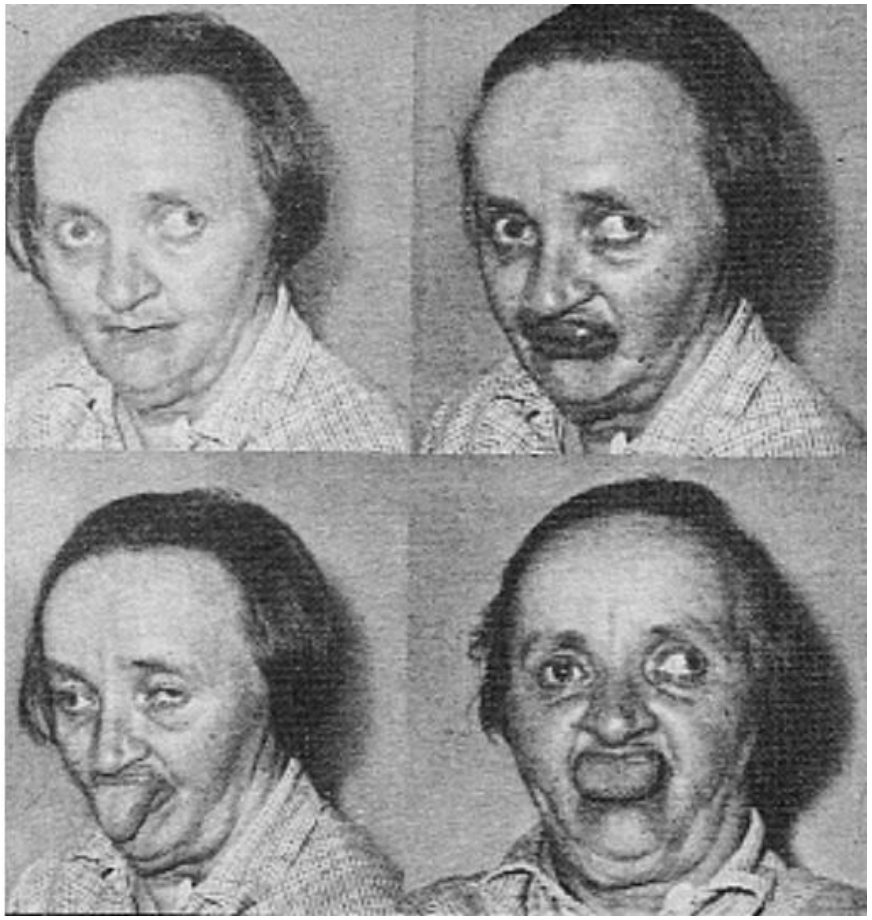
Akathisia

- Motor restless or the inability to sit still
- Sign: pacing, shifting, shuffling, foot tapping, inner restlessness

Treatment

Propranolol
Or
Benzodiazepine
(lorazepam)

Tardive Dyskinesias



Treatment – PREVENTION and MONITORING

May be permanent

Atypical Antipsychotics

- Clozapine (Clozaril)
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Paliperidone (Invega)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)

- Aripiprazole (Abilify)

New in 2010-2011

- Asenapine (Saphris)
  - Dissolved under the tongue
- Iloperidone (Fanapt)
- Lurasidone (Latuda)

Atypical Side Effects

- **Weight gain**
- **Lipid abnormalities**
- **Glucose intolerance / Diabetes**
- Arrhythmias

Weight Gain, Diabetes, Lipids

- More prominent with atypical AP
- Clozapine > olanzapine > quetiapine > risperidone > ziprasidone=aripiprazole
- Weight gain of up to 25-50 pound is common with clozapine

Clozapine (Clozaril)

- Reserved for treatment resistant patients
- Reduces the risk of suicide in Schizophrenia
- Many Side effects
  - **Agranulocytosis**
  - **Seizures at doses > 600 mg/day**
  - Orthostatic hypotension – must titrate slowly
  - **Myocarditis**
  - **Sedation**
  - Weight gain, diabetes
  - Sialorrhea (excessive drooling)

Efficacy of Antipychotics in Dementia

Atypical Antipsychotics

- Most studied for behaviors related to dementia
- Most commonly used in clinical practice
- Better tolerated than typical antipsychotics
- Lower risk of EPS but there is still a dose-dependent risk
- Metabolic syndrome (wt gain, DM, Lipids)

Efficacy of Antipychotics in Dementia

- CATIE-AD
  - Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) – Alzheimer's Disease
  - No significant benefit (p=0.22) with modest treatment using atypical antipsychotics for behaviors related to dementia
  - Olanzapine, risperidone, and quetiapine had marginally higher response rates (32%, 29%, and 26%, respectively) than placebo (21%)

Schneider LS, et al. 2006 NEJM; 355: 1525-38

Systematic Review

- Reviews of double-blind, placebo-controlled RCTs or meta-analyses
- Pharmacotherapy had modest improvement of symptoms
  - At best 20% more patients respond to antipsychotics then placebo
- However, small improvements may benefit the patient and caregiver.
- Studies recommend to discontinue treatmet after 8-12 weeks

JAMA 2005 Feb 2;293(5):596-608

Evidence for Efficacy of AP in Dementia

	Aripiprazole (Abilify)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)
Overall	++	+	+	++
Psychosis	+	+/-	+/-	++
Agitation	+	++	+/-	++

++ = moderate or high evidence of efficacy
+ = low or very low evidence of efficacy
+/- = mixed results

Carahan, R. Antipsychotics Use in Dementia. Iowa Generic Center
https://www.healthcare.uiowa.edu/igec/iaadapt/

Antipsychotic Side Effects in Older Adults

- Older individuals are more sensitive to side effects, even at low dosages
- Hard for older adults to express side effects

Common Side Effects of Atypical AP in Older Adults

- Sedation (up to 25%)
- Confusion (up to 18%)
- Risperidone – EPS common (12%)
  - Least with quetiapine
- Weigh gain – 0.5 – 1pound/month

Antipsychotic Side Effects Comparison

	Haloperidol (Haldol) (0.25-2mg)	Aripiprazole (Abilify) (2-10 mg)	Olanzapine (Zyprexa) (2.5-7.5mg)	Quetiapine (Seroquel) (12.5-150 mg)	Risperidone (Risperdal) (0.25-2 mg)
Movement SE	+++	++	++	+	++
Sedation	++	++	+++	++++	++
Confusion, delirium, cognitive worsening	-	+	++	+	+
Worsening psychotic symptoms	-	-	+	-	-

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Antipsychotic Side Effects Comparison

	Haloperidol (Haldol) (0.25-2mg)	Aripiprazole (Abilify) (2-10 mg)	Olanzapine (Zyprexa) (2.5-7.5mg)	Quetiapine (Seroquel) (12.5-150 mg)	Risperidone (Risperdal) (0.25-2 mg)
Orthostatic hypotension	++	+?	+	+?	+?
Edema	-	+?	+	-	++
Weight gain/ Diabetes	+?	-	+++	+	++
↑ Cholesterol	-	-	++++	+++	-
Urinary Incontinence	++	+++	++	++	++

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Dangerous or Severe Side Effects in Older Adults

- Stroke
- Pneumonia
- Tardive Dyskinesia
- DEATH

Stroke

- Conflicting Data
- 4 trials with risperidone (0.5 – 2 mg/d) for treatment of BPSD for 8-12 weeks
- Incidence of stroke was 3.4 % for risperidone versus 1.2 % placebo
- Many weaknesses of this data to make a causal relationship
- Additional studies support these findings

Black Box Warning
Mortality: Antipsychotics

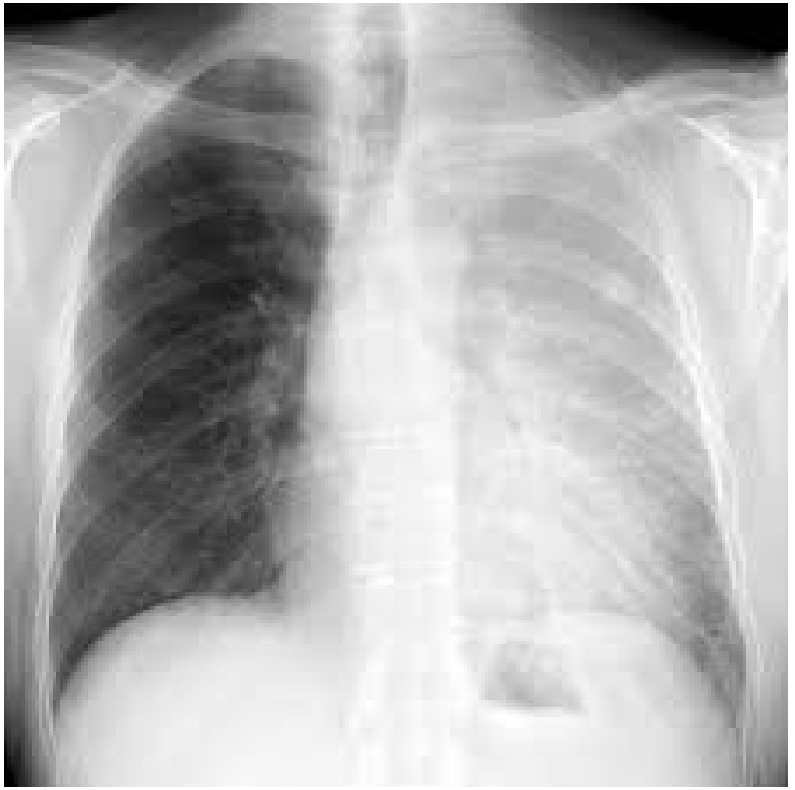
- **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**– Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. This drug is not approved for the treatment of dementia related psychoses.

Mortality: Antipsychotics

- Meta-analysis of 15 studies in patients with dementia
- ~1.6-1.7 fold increase in mortality in active treatment over placebo
- Most deaths cardiovascular or infectious
- Risks did not differ among agents studied (aripiprazole, olanzapine, quetiapine, risperidone)
- Most studies were short-term (< 3 months)
- Extended to all antipsychotics in June 2008

Pneumonia?

- How do antipsychotics cause pneumonia?
- Theoretical explanations
  - Swallowing dysfunction
  - Increase aspiration due to impaired cough reflex
  - Sedation – increase aspiration?



Tardive Dyskinesia

- Severe, disabling and can be irreversible
- Occurs more often in older adults
- Occurs less often with atypicals compared to typicals
  - Haloperidol 25% vs Risperidone 2.6% at 1 year
- May lead to chewing and swallowing difficulties
- May result in feeding tubes

Monitoring for Antipsychotic Response

- Identify 1-2 of the most troubling symptoms
- Need to be specific and objective as possible when documenting problems, behaviors and psychotics symptoms
  - Agitation ≠ good descriptor
  - Hitting, kicking or biting – more specific
  - Document circumstances surrounding behaviors for clues on what triggers behaviors

Monitoring for Antipsychotic Response

- Clearly document
- Do not expect an immediate response
- Do not ask for higher doses too quickly
  - Higher doses cause more side effects

Monitoring of Side Effects

	Monitoring
Sedation	Sleepiness, slow to respond, hard to wake up - Administer a sedation scale
Confusion, delirium, cognitive worsening	Worsening confusion, communication abilities or ↑ agitation Slower movements or speech Problems paying attention - Administer delirium screening tool - CAM (Confusion Assessment Method)
Worsening psychotic symptoms	Hallucination – auditory, visual, tactical, olfactory Delusion – fixed, false belief
Tardive Dyskinesia	Abnormal Involuntary Movement Scale (AIMS) baseline and every 3-6 months

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Monitoring of Side Effects

	Monitoring
Cardiovascular	ECG
Orthostatic hypotension	Signs of dizziness and increase falls
Edema	Swelling -- Most common in legs and ankles
Weight gain/ Diabetes	↑appetite Hungry after eating Unwanted weight gain - Monitor weight monthly
High blood sugars	↑ blood sugars, Confusion, ↑ thirst, ↑ urination Blurred vision - Order FBS at baseline, 12 weeks and every 6months and as needed based on symptoms
Death, Stroke, Pneumonia	No risk reduction strategies Identify Individual Risk Factors

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Dosing and Administration

- Start low and go slow
- Most AP are dosed once daily at bedtime
- Oral disintegrating tablets
- Regular – release tablets can be crushed and mixed with foods
- Sun downing – dose in evening prior to onset of symptoms

Antipsychotics Dosing and Dosing Forms

	Starting Dose (mg/day)	Maximum Maintenance Dose	Special Dosage Forms
Haloperidol	0.25	2	Liquid Short Acting IM
Aripiprazole	2-5	10	Orally dissolving tablet Liquid Short Acting IM
Olanzapine	2.5-5	7.5	Orally dissolving tablet Liquid Short Acting IM
Quetiapine	12.5-25	150	Extended Release
Risperidone	0.25-0.5	2	Orally dissolving tablet Liquid

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Dosing and Administration

- **ONLY CONTINUE TREATMENT IF EFFECTIVE**
- After 12 weeks of treatment consider a trial off
- If BPSD reoccurs and are not manageable with non-drug treatment consider restarting antipsychotic

Gradual Dose Reductions

- Within 1st year after admission on antipsychotic or after initiation
  - GDR in 2 separate quarters, with at least one month between attempts
- After 1st year:
  - GDR annually
- GDR is clinically contraindicated if: resident's target symptoms returned or worsened after most recent GDR attempt within facility and MD has documented clinical rationale

Other Options for BPSD

- Cholinesterase Inhibitors
- Memantine
- Anticonvulsants
- Antidepressants
- Benzodiazepines
  - Worsen confusion and increase risk of falls

Summary

- Non-drug therapy should be initiated first
- No drug specifically addresses wandering, hoarding, or resistance to care
- Modest benefit from antipsychotics
- Remember BPSD symptoms wax and wane
- Many AP are sedating and increase the risk of falling and injury. Need to monitor for sedation
- Family and Caregivers need to be educated about the risks of antipsychotics