This presentation will include discussion of off-label uses of medications.

Objectives

Using a case study approach:

1. Describe less common complications of psychotropic medications when using them with older adults.
2. Identify risk factors and strategies for early identification for these complications.
3. Develop appropriate treatment plans to manage complications of psychotropic medications with older adults.
Approximately 8 million older adults in the US have mental illness.
This number is expected to double to 15 million by 2030.

- American Association of Geriatric Psychiatry (2012)

Psychotropic drug use as high as 70% among nursing home residents
- (Rolland et al., 2012; Kim & Whall, 2006).

Use is greater among:
- Older women
- Residents with dementia
- Residents with functional disability
- Facilities with low levels of RN staffing
Older Adults and Pharmacotherapy

- Older adults over the age of 75, are often excluded from clinical trials making application of findings challenging
- Age related decline in liver and kidney function
- Issues related to multi-morbidity (drug–disease interactions) and drug–drug interactions
- Polypharmacy

American Society of Consultant Pharmacists (2014)

Leads to increased risk of adverse drug events

Case 1
Case 1 (Mrs. G)

- 83 year old married white female
- Long history of bipolar disorder, type II and three year history of vascular dementia
- Lives at home with her husband and daughter and son live nearby
- Functionally, she is able to perform her ADLs with encouragement/cueing; she ambulates with a cane, helps to prepare simple meals with supervision, communicates effectively
- MMSE = 23

Case 1 (continued)

- Medical history is notable for HTN, hyperlipidemia, CAD, vascular dementia
- History of tobacco use; though doesn’t currently smoke
- Medications: ASA, Atenolol, Lisinopril, Atorvastatin, Methylphenidate 10 mg BID, Olanzapine 5 mg QHS, Fluoxetine 40 mg QD, Lithium Carbonate 300mg QD, Donepezil 10mg QHS

Case 1 (continued)

- Her outpatient provider receives a call from her husband and reports that Mrs. G had a stroke with left sided weakness. She was doing well in her rehabilitation stay but now she is:
  - more confused
  - unable to stand and walk
  - exhibits intermittent, uncontrolled jerking of her limbs, particularly her legs
  - agitated and irritable
  - exhibits some tremor
The provider calls the nurse practitioner who is caring for Mrs. G. in rehabilitation and she confirms the symptoms that the husband reports. Mrs. G’s labs are normal and she has been treated for a UTI.

The NP asks if any of her psychiatric medications could be causing these symptoms?

What could be causing the symptoms?

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Serotonin Syndrome

A potentially life-threatening condition caused by excessive serotonergic activity in the nervous system.

Incidence: 0.4 cases per 1000 patient-months of antidepressant treatment.

Classical clinical features:
- Mental status changes
- Autonomic instability
- Neuromuscular hyperactivity
Etiology of Serotonin Syndrome

- Iatrogenic from synergistic medication use
- Intentional self-poisoning with serotonergic agents (rare)
- Addition of drugs that inhibit the cytochrome P450 and CyP3A4
- Can emerge from an overdose, therapeutic doses, or single agent use

Mechanisms of Serotonin Syndrome (Increased 5-HT in CNS)

- Increased availability of the 5-HT precursor, L-tryptophan
- Increased release of 5-HT caused by amphetamines, dextromethorphan, opioids
- 5-HT reuptake inhibition by antidepressants and tramadol
- Decreased metabolism of 5-HT by MAOIs
- Postsynaptic 5-HT receptor agonism from triptans, lithium, carbamazepine

Mechanisms of Increased 5-HT
Medication Classes that May Contribute to Serotonin Syndrome

- Amphetamines and derivatives
  - Ecstasy, cocaine, methamphetamine
- Analgesics
  - Cyclobenzaprine (Flexeril), fentanyl (Duragesic), meperidine, tramadol
- Antidepressants/mood stabilizers
  - Lithium, MAOIs, SSRIs, SNRIs, Tricyclics, trazodone
- Antiemetics
  - Metoclopramide (Reglan), ondansetron (Zofran)
- Anti-migraine drugs
  - Ergot alkaloids, triptans, carbamazepine, valproic acid
- Miscellaneous
  - Dextromethorphan, L-tryptophan

Signs & Symptoms

- Mental status changes
  - Agitation, anxiety, confusion, euphoria
- Autonomic instability
  - Fever, tachycardia, hypertension, tachypnea, diaphoresis, diarrhea
- Neuromuscular hyperactivity
  - MYOCLONUS, tremor, akathesia, rigidity, hyperreflexia, clonus, ataxia, altered coordination usually more marked in the lower limbs

Treatment

- Prevention
  - Avoid more than one medication with serotonergic activity
  - Consider half life (sertraline=26 hours versus fluoxetine 96–144 hours with chronic use)
- Management
  - Prompt withdrawal of the serotonergic drugs
  - May require hospitalization (hypertonicity, hyperthermia, autonomic instability, cognitive changes)
  - Benzodiazepines for agitation and tremor
  - Cyproheptadine (serotonin 2A antagonist) most widely used antidote: 12mg initial dose, followed by 2mg Q2 hours until symptoms remit
Case 2

- 87 year old woman who is the resident of an assisted living facility
- Treated for depression with Citalopram 20mg PO QD
- She becomes progressively lethargic and later confused over the next two weeks (wanders into a peer's apartment, misses dinner) and is distractible.
- A urinalysis and culture and sensitivity are negative.
- She had some mild memory problems at baseline (MMSE=26), but now her score is 15.

What could be causing her symptoms?
Hyponatremia induced by SSRI

SSRIs are widely used among older adults
- Good safety margin
- Manageable dosing and titration guidelines
- Low risk of anticholinergic and cardiovascular effects

Common Side Effects of SSRIs
- Sedation
- Agitation
- GI upset
- Sexual dysfunction
- Weight loss (early)
- Weight gain (chronic use)
### Signs & Symptoms of Hyponatremia

- Serum sodium < 135 mEq/L
- Thirst
- Anorexia
- Muscle cramps
- Headache
- Lethargy
- Hyporeflexia
- Confusion
- Seizures
- Coma

#### Early signs/less decrease in sodium

- Thirst
- Anorexia
- Muscle cramps
- Headache
- Lethargy

#### Later signs/lower sodium

- Hyporeflexia
- Confusion
- Seizures
- Coma

### Risk factors for hyponatremia among older adults

- Previous history of hyponatremia
- Use of thiazide diuretics
- Medical co-morbidities (pneumonia)
- ETOH use
- Female gender
- Older age
- Low body weight

### Older adults are at particular risk of hyponatremia due to physiologic changes related to aging

- Reduction in total body water
- Decreased renal perfusion
- Decreased glomerular filtration rate
- Diminished renal tubular concentration capability
- Impaired diluting potential
Mechanism of Hyponatremia associated with SSRIs

- Not well understood
- May occur secondary to SIADH
  - Serotonin can increase or sustain antidiuretic hormone (ADH) secretion
  - This results in water retention and dilutional hyponatremia

Management of Hyponatremia Associated with SSRIs

- Discontinue offending agent (2 weeks for sodium levels to normalize)
- Fluid restriction
- Mild diuresis with a loop diuretic
- Intravenous normal saline (only in the presence of concurrent dehydration)
- Consider atypical antidepressants (mirtazapine, trazodone, bupropion)
Case 3

- 70 year old married woman who has a history of early onset Alzheimer's disease that was diagnosed when she was 59 years old.
- Her course has been complicated by neuropsychiatric symptoms, most notably depression and agitated behaviors.
- She has had 2 previous psychiatric hospitalizations in the context of her dementia.

Case 3 (continued)

- Her medications include Sertraline 100mg QD; Depakote 250 mg in the am and 500 mg QHS for dementia with behavioral symptoms; and Clonazepam 0.25 mg BID.
- She has a history of intolerance to antipsychotics.
- The resident had been stable on this medication regimen for 9 months except for gradual dose reduction of Clonazepam.
- Her last Clonazepam reduction was 2 months ago.

Case 3 (continued)

- The nursing staff asked for the resident to be evaluated after 5 days of increased confusion, and calling out.
- The resident's labs included a CMP, CBC, VPA level, ammonia level, and U/A and C&S.
- All were normal including AST and ALT and VPA level of 65 except for ammonia level of 90 ug/dL.

What is happening with this resident and what should be done?
90% of individuals with dementia will develop behavioral symptoms at some point during the course of their illness

No FDA approved medications

Shift away from antipsychotics

Used to treat behavioral symptoms in dementia since 1986

Conflicting evidence on efficacy

Lethargy

Thrombocytopenia

Ataxia

Weight gain

Liver toxicity
VPA Induced Hyperammonemia

- A metabolic disorder characterized by an excess of ammonia in the blood that leads to progressive loss of neuronal function
- Can occur after both acute overdose and while on therapeutic chronic dose of VPA
- Commonly occurs with normal LFTs & VPA levels (independent of hepatotoxicity)
- Asymptomatic in almost 50% of cases

Symptomatic VPA Induced Hyperammonemia

- Acute onset of impaired consciousness
- Disorientation
- Cognitive slowing
- Possible focal neurologic findings
- Vomiting
- Anorexia
- Seizures
- Generalized slowing on EEG

Challenging to Diagnose

- Challenging to diagnose among older adults and psychiatric patients due to multiple possible causes of mental status changes
- Laboratory transport time may skew results
Possible Mechanisms of VPA Induced Hyperammonemia

- VPA increases ammonia production in the kidneys by enhancing uptake of glutamine and/or increasing glutaminase activity
- VPA reduces ammonia metabolism in the liver, possibly by decreasing carnitine availability (in the urea cycle)

Risk factors for VPA Encephalopathy

- Treatment with VPA for long durations
- Treatment with other anticonvulsants

Treatment of VPA Induced Hyperammonemia

- Decrease dose of VPA (may not always be dose dependent)
- Discontinue VPA
- Carnitine
Case 4

- 76 year old man with dementia probable Alzheimer’s disease diagnosed 5 years ago
- Lives at home with his wife and attends a medical adult day program
- History of delusions and physically aggressive behaviors that resolved with Olanzapine 2.5 mg PO BID that he has taken over the past 3 months.
- He also takes Sertraline 50 mg QD and Donepezil 10 mg QHS

Case 4 (continued)

- His wife takes him to the emergency room when he develops increasing confusion, low grade fever, increased tone, and lethargy
- He is admitted to the hospital and diagnosed with ?????
- What else should be considered?
Neuroleptic Malignant Syndrome (NMS)

- Severe, potentially lethal reaction to neuroleptics (conventional and atypical)
- Rare (0.07% to 3.23%) of individuals treated with neuroleptics
- Severity and lethality is less in atypical antipsychotics

Symptoms of NMS

- Fever
- Autonomic instability (tachycardia, hypertension/labile BP)
- Altered mental status
- Rigidity and other movement disorders (tremor, dystonia, myoclonus)
- Substantial variation
Laboratory Findings Associated with NMS
- Elevated creatine phosphokinase
- Leukocytosis
- Renal impairment
- Altered liver function tests

NMS
- All dopamine Blocking drugs are capable of precipitating NMS
- Abrupt withdrawal of dopaminergic agonist drugs used to treat Parkinson's disease, such as levodopa and amantadine may result in NMS like conditions

Risk Factors for NMS
- Exposure to high affinity D2 receptor drugs
- Presence of psychomotor agitation
- Use of long acting depot antipsychotics
- Higher dosage of antipsychotics
- Neuroleptic polypharmacy
- Previous history of NMS
- Concurrent lithium and neuroleptics
Treatment

- Supportive in nature
  - Fluid replacement
  - Fever reduction
  - Support of cardiac, respiratory and renal function
- Discontinuation of antipsychotic
- Benzodiazepines for tremor/rigidity
- Avoid rechallenge with antipsychotics