

# Common Drug-drug and Drug-disease interactions in Hospice

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## Objectives

- ▶ Identify common interactions found in hospice patients
- ▶ Point out clinical presentations of these interactions.
- ▶ Understand when to discontinue meds vs when to continue
  - Identify the risks vs benefits of continuing
  - Know drug of choice

## Background information on hospice

- ▶ Terminal dx
  - Pertinent meds needed for care and to Palliate symptoms
- ▶ Comorbidities
  - Palliative
  - Non-Palliative
    - ◆ Recommend D/C to avoid multiple interactions

## Common interactions in hospice

Drug-Drug Interactions	Drug-Disease
Serotonin syndrome	Antipsychotics in Parkinson's disease
QT prolongation	Use of NSAIDs in CHF patients
Drug induced Hyperkalemia	Meds that increase bleeding risk in hospice patients
Multi Opioid use	

## Serotonin Syndrome

- ▶ Occurs due to overstimulation of serotonin receptors
  - Central
  - Peripheral
- ▶ Under diagnosed due to symptoms being non-specific
- ▶ Can occur due to different mechanisms
  - Increase serotonin production
  - Decrease serotonin reuptake
  - Stimulation of receptors

## Serotonin Syndrome contd.

- ▶ Occurs within few hours to 24 hours of:
  - Increase in the serotonergic agent
  - Overdose
  - Addition of Serotonergic agent
- ▶ Causative agents
  - Antidepressants - Celexa, Prozac, Duloxetine, Effexor, Amitriptyline
  - Pain meds - Tramadol, Fentanyl IV
  - MAO-I - Isocarboxazid, Phenelzine, Selegiline, Tranylcypromine
    - ◆ (biggest culprit, allow for 2 week washout)
  - Supplements - St. John's wort, ginseng, nutmeg
  - Antinausea - Metoclopramide, Zofran

## Serotonin Syndrome clinical presentation

Mental Status	Agitation, Confusion, Delirium, Hallucinations
Neuromuscular	Hyperreflexia, Increased muscle tone, Rhabdomyolysis, Rigidity, Shivering
Autonomic	Diarrhea, Mydriasis, Fever, Flushing, Increased bowel sounds, Increased respiratory rate

## Serotonin Syndrome -Management

- ▶ Mild Symptoms
  - Resolve within 24 to 72 hours
  - Diarrhea, sweating, shivering
  - Drug discontinuation, Benzodiazepine (reduce tonic) and supportive care
- ▶ Moderate to Severe
  - Rapid increase in temperature and muscle rigidity
    - ◆ Medical emergency
    - ◆ Multi-organ failure
    - ◆ Antipyretics not recommended
  - D/C causative agents
  - May need sedation or intubation

## QT Prolongation

- ▶ Life threatening arrhythmia associated with prolongation of QT interval
  - Can lead to torsades de pointes
- ▶ Risk factors
  - Advanced age
  - Female Sex
  - Acute MI
  - Heart failure with reduced ejection fraction
  - Hypokalemia/Hypomagnesemia
  - Drug-drug interactions
  - Inadequate dose adjustment in patients with renal/hepatic failure
  - Genetic predisposition

## QT prolongation

- ▶ Signs/symptoms
  - Abnormal heart rhythms
  - Bradycardia
  - Syncope
  - Light headedness
  - Seizures
  - Sudden death
- ▶ Causative drugs (commonly found in hospice patients)
  - Antiarrhythmics (Amiodarone, Sotalol)
  - Antimicrobials (Fluoroquinolones, Macrolides, Bactrim)
  - Antipsychotics (Haldol, Risperidone, Chlorpromazine)
  - Anti-nausea (Zofran, Reglan, Promethazine)
  - Opioids (Methadone)
  - Antidepressants (Fluoxetine, Amitriptyline, Sertraline, Duloxetine)

## QT prolongation – Prevention/Management

- ▶ ECG Monitoring (not commonly done in hospice)
- ▶ D/C causative agents
  - Unless compelling reasons to continue
- ▶ Monitor serum Potassium, Magnesium and Calcium
- ▶ High risk meds
  - Prescribe alt. non-QT prolonging drugs
- ▶ Adjust drug dose in patients with kidney disease
- ▶ Avoid QT prolonging drugs in patients with Heart failure and LVEF < 20%
- ▶ Avoid QT drugs in patients with a Hx of drug induced torsades de pointes

## Drug induced Hyperkalemia

- ▶ Hyperkalemia results from
  - Increased intake of Potassium
  - Reduced excretion of Potassium
- ▶ Life threatening
  - Levels >5.5mmol/L
- ▶ Causes
  - Acute/chronic renal failure
  - Drug-drug interactions
  - Rhabdomyolysis
  - Hypoaldosteronism

## Drug induced hyperkalemia contd.

- ▶ Symptoms of Hyperkalemia
  - Muscle weakness
  - Irregular heart beat (palpitations)
  - Feeling too tired
  - Tingling sensation
  - Fainting
  - Muscle pain
- ▶ Meds that cause Hyperkalemia
  - Spironolactone and ACE inhibitor combination
    - ◆ Seen in patients with HF and increased renal impairment
    - ◆ Careful monitoring
  - Blood pressure meds (ARBs/Beta blockers/Calcium channel blockers)
  - NSAIDs in renal failure/diabetes
  - Trimethoprim
  - Supplements

## Management of Hyperkalemia

- ▶ Mild symptoms
  - Muscle weakness, tiredness, tingling sensation, nausea
  - Identify and eliminate source of Potassium intake
    - ◆ Drugs
    - ◆ Diet
  - Administer Kayexalate
  - Don't require ICU/hospital stay
- ▶ Moderate to Severe
  - Signs of heart attack
    - ◆ Call 911
  - ECG monitoring
    - ◆ Not common practice in hospice

## Multi opioid use

- ▶ Opioids are used for the management of severe chronic pain
- ▶ Breakthrough pain and intermittent pain
  - Use short acting opioids
  - Eg. Roxanol, Oxycodone
- ▶ Continuous pain
  - Long-acting and sustained release opioids
  - Eg. Fentanyl, MS Contin
- ▶ Used in combination with non-opioids
  - Permits use of lower doses of opioids

## Multi Opioid use

- ▶ Prescribing errors with opioids in palliative care
  - Failure to prescribe Around-the-clock opioids for constant pain
    - ◆ Use of multiple short acting opioids prn
    - ◆ Long-acting opioids preferred to create more stable serum levels
    - ◆ Using incorrect dosing intervals leading to fluctuating serum levels
  - Use of multi opioids and formulations
    - ◆ Leads to accumulation and toxicity
- ▶ Use with caution in patients with impaired ventilation, bronchial asthma and liver failure

## Side effects of multi opioid use

- ▶ Sedation
- ▶ Confusion
- ▶ Respiratory depression
- ▶ Pruritus (itching)
- ▶ Nausea and vomiting
- ▶ Constipation

## Management of opioid side effects

- ▶ Monitor respiration status during first 24 hours of treatment in opioid naive patients
  - Stop opioid use until respiratory depression resolves and start at 75% of previous dosage
  - Administer naloxone if patient is minimally unresponsive or unresponsive
  - Use Spirometry and oxygen as needed
- ▶ Titrate drug doses slowly
- ▶ Consider changing dosing regimen to obtain constant blood levels
- ▶ Add nonopioid or adjuvant analgesic
- ▶ Consider switching to another opioid
- ▶ Assume constipation will develop and treat for it
- ▶ Consider use of antihistamines for pruritus

## DRUG-DISEASE INTERACTIONS

## Antipsychotics in Parkinson's

- ▶ Psychosis is found to be very common in patients with Parkinson's
  - Usually seen in later stages (>5.5 years)
- ▶ Exposure to PD meds over years leads to psychosis
  - L-dopa, dopamine agonist, MAO, anticholinergics
- ▶ Treatment with certain antipsychotics can worsen disease
  - Leads to drug-induced extrapyramidal symptoms (EPS)

## Clinical presentation of EPS

- ▶ Dyskinesias and dystonic reactions
- ▶ Tardive dyskinesia
- ▶ Parkinsonism
- ▶ Akinesia
- ▶ Akathisia
- ▶ Neuroleptic malignant syndrome.

## First Generation Antipsychotics in Parkinson's

- ▶ Worsen Parkinson's symptoms therefore should be avoided
  - Induce significant movement disorders such as bradykinesia, tremor and rigidity
  - Anticholinergic side effects
    - Constipation, urinary retention or dry mouth
  - Sedation
  - Orthostatic hypotension
- ▶ Drugs in this class include
  - Haloperidol, Chlorpromazine

## Second generation Antipsychotics

- ▶ Less risk of worsening extrapyramidal symptoms
- ▶ Safety profiles differ amongst members in this class
  - Majority have cardiometabolic effects which include:
    - Weight gain, dyslipidemia, hypertension, increased insulin resistance
    - Avoid Clozapine and Olanzapine in patients with diabetes, obesity or dyslipidemia
    - Avoid Clozapine and Ziprasidone in patients with Heart failure and QTc prolongation
- ▶ Drugs in this class include:
  - Seroquel, Risperidone, Clozapine, Olanzapine

## Treatment contd.

- ▶ Antipsychotics of choice
  - Pimavanserin
    - \$\$\$
    - Does not block dopamine
  - Clozapine
    - Low dose
    - Was once considered drug of choice for psychosis in PD
    - Side effects of agranulocytosis
    - Patients required to get frequent blood tests
  - Quetiapine
    - Low doses
    - 1<sup>st</sup> choice
    - Side effect profile of sedation with higher doses
  - Olanzapine and Risperidone
    - Atypical antipsychotic
    - Still have a risk of aggravating PD

## Management of EPS symptoms

- ▶ Taper off offending antipsychotic and D/C
  - Monitor patient closely for improvement in symptoms/exacerbation of psychotic symptoms
  - May require adding using Benzo, Dopamine agonists, or anticholinergic
- ▶ Switch to atypical antipsychotic/use lowest effective dose
  - Seroquel, Risperidone, Olanzapine

## NSAIDs in CHF

- ▶ NSAIDs stand for Non-steroidal anti-inflammatory drugs
  - Ibuprofen, Meloxicam, Celecoxib
- ▶ Clinical guideline discourage use in CHF patients
  - American heart association
  - Patients with high risk of cardiovascular disease
  - COX 2 > COX 1
- ▶ Cause fluid retention or reduced cardiac function
  - US boxed warning
  - Increased risk of cardiovascular thrombotic events
  - Risk seen at higher doses

Table 1. NSAID Selectivity

More COX-1 Selective	Nonselective	5-50-fold COX-2 selective*	>50-fold COX-2 selective*
Ketorolac (Acular) Flurbiprofen (Kofurol) Ketoprofen (Generics) Indometacin (Indocin) Aspirin (Generics) Naproxen (Anex) Tolmetin (Genvion) Piroxicam (Feldene) Meclofenamate (Generics)	Ibuprofen (Advil, Motrin) Fenoprofen (Nalfon) Sodium salicylate (Generics) Diflunisal (Generics)	Sulindac (Clinoril) Diclofenac (Cambia) Celecoxib (Celebrex) Meloxicam (Mobic) Etoricoxib (Generic)	Etoricoxib (Acoxia) Lumiracoxib (Prexige)

← Increased gastrointestinal effects      Increased cardiovascular effects →

\*Listed in order of increasing COX-2 selectivity  
 \*Equivalent for COX-1 and COX-2 selectivity  
 †At higher doses, COX-2 selectivity decreases and COX-1 inhibition increases†  
 ‡Not yet approved by the FDA

COX, cyclooxygenase; FDA, Food and Drug Administration; NSAID, non-steroidal anti-inflammatory drug

Ask the Expert: Which NSAIDs are Most Selective for COX-1 and COX-2?  
<https://www.practicalpainmanagement.com/treatments/pharmacological/non-opioids/ask-expert-which-nsaids-are-most-selective-cox-1-cox-2>

## NSAIDs in CHF

- ▶ Interaction with loop diuretics
  - Most CHF patients on loop diuretics
  - Patients have reduced renal function
  - NSAIDs cause Na and H<sub>2</sub>O retention
    - ◆ Negates effects of loop diuretics
- ▶ Clinical presentation
  - New onset HTN
  - Worsening fluid retention
    - ◆ Weight checks
    - ◆ Use with caution in patients with hx of edema
  - Hyperkalemic state
    - ◆ Monitor of Sx of hyperkalemia
  - Renal injury
  - GI bleeds

## NSAIDs in CHF – Management of Sx

- ▶ D/C NSAIDs
  - Evaluate the risks vs. benefits
- ▶ If NSAIDs are desired
  - Non-selective NSAIDs are preferred
    - ◆ Ibuprofen and Naproxen (avoid using high doses for a long period of time)
    - ◆ Have more GI side effects therefore use with PPI
- ▶ Consider Acetaminophen or other weak opiates

## Bleeding risk in hospice patients

- ▶ Hospice providers decide when or when not to continue anticoagulant therapy
  - Weigh risks vs benefits of continuing
  - Prophylaxis vs treatment?
- ▶ Anticoagulants used for patients who are symptomatic
  - Relief of chest pain
  - Dyspnea
  - Painful swelling of lower extremities

## Bleeding risk in hospice patients

- ▶ Factors that increase risk of bleeding
  - Hospice patients most often in a debilitated state
    - ◆ Increased risk of fall
    - ◆ Multiorgan failure
    - ◆ Reduction in renal or hepatic function
      - ▶ Reduces metabolism/elimination of drug
      - ▶ Reduction in clotting factors
  - Reduced nutritional intake
    - ◆ Reduced production of clotting factors
  - Multiple co-morbidities
    - ◆ Hx of GI bleed, low hematocrit, on other meds that increase bleeding

## Bleeding risk in hospice patients

- ▶ Clinical presentation
  - Blood in urine
  - Dark stools
  - Nose bleeds
  - Vomiting or coughing up blood
  - Bleeding gums
  - Purple/blue bruise on body

## Bleeding risk in hospice patients

- ▶ Medications include
  - Anticoagulants – Warfarin, Lovenox
  - Antiplatelets – Plavix, Aspirin
  - NSAIDS
  - Antidepressants (SNRI and SSRI)
  - Supplements e.g. Gingseng, Garlic, Gingko, Fish oil.
- ▶ Management
  - Patient education
  - Report falls
  - Decision to stop meds usually made by attending physician.



Questions