PALLIATIVE PEARLS
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Drug Interactions in Hospice: Important Considerations Guidance
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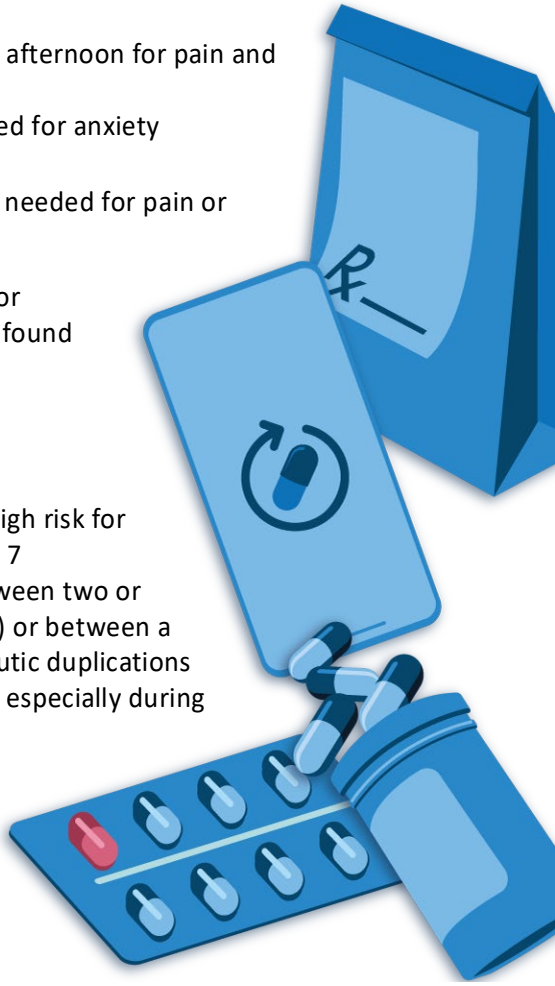
PATIENT CASE

TS is a 68-year-old male diagnosed with advanced non-small cell lung cancer a year ago. He recently enrolled in hospice after discontinuing chemotherapy due to extreme fatigue and disease progression. TS has no significant past medical history, no known drug allergies, and lives at home with his wife who is his primary caregiver.

MEDICATIONS

- Albuterol 0.083% solution; Inhale 1 amp via nebulizer every 4 hours as needed for shortness of breath
- Dexamethasone 4mg tablet; 1 tablet by mouth every morning and afternoon for pain and appetite
- Lorazepam 0.5mg tablet; 1 tablet by mouth every 4 hours as needed for anxiety
- Methadone 10mg tablet; 1 tablet by mouth every 8 hours for pain
- Morphine (Roxanol®) 20mg/ml; 0.25ml by mouth every 3 hours as needed for pain or shortness of breath



Over the past few days, his wife reports that TS is not interested in eating or drinking due to mouth pain and discomfort chewing and swallowing. He is found to have sores and white patches in his mouth indicative of oropharyngeal candidiasis (oral thrush).

INTRODUCTION

The terminally ill adult may possess several attributes that place them at high risk for drug interactions. These include advanced age, regular use of greater than 7 medications and multiple comorbidities.1 Drug interactions can occur between two or more drugs (drug-drug), between a drug and a disease state (drug-disease) or between a drug and food/drink (drug-food). It's important to also be wary of therapeutic duplications (prescribing 2 or more medications unnecessarily for the same indication), especially during transitions of care and managing formulary-related substitutions.

Because of the growing number of medications marketed, it would be a daunting task to remember all possible drug interactions. Recognizing patient attributes that place them at risk for drug interactions and several of the common culprits will put you in good shape as you develop patient care plans. Lean on your pharmacy team for

the rest! This case will explore some clinically significant drug interactions requiring clinician intervention and ways to manage. This review however is not comprehensive and does not replace regular drug-utilization reviews and clinician collaboration.

CLINICALLY SIGNIFICANT INTERACTIONS

1. QT Prolongation

Long QT syndrome (LQTS) is a disorder of cardiac repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG).[2] LQTS can be congenital or acquired and is associated with an increased risk of polymorphic ventricular tachycardia, also known as torsades de pointes (TdP). TdP is a type of arrhythmia that, while rare, is life-threatening thus warrants attention and recognition of precipitating risk factors. Drug-induced LQTS is the most common type and can be categorized as drug-drug or drug-disease.[2,3]

Known medication culprits (See CredibleMeds® for a comprehensive list):[4]

- Antiarrhythmics: Class IA agents (e.g., quinidine, disopyramide, procainamide) and Class III agents (e.g., sotalol, dofetilide, amiodarone)
- Antimicrobials: Fluoroquinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin), macrolides (e.g., erythromycin, azithromycin), and antifungal agents (e.g., fluconazole (Diflucan®), ketoconazole, itraconazole)
- Conventional antipsychotics (e.g., haloperidol, chlorpromazine, thioridazine)
- Donepezil (Aricept®)
- Methadone
- Ondansetron (Zofran®)
- Selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram (Celexa®), escitalopram (Lexapro®))

Common disease state culprits:[5,6]

- Prolonged QTc > 500 msec
- Congenital LQTS
- Age > 65 years
- Female gender (baseline QTc are generally 20 milliseconds greater than males)
- Heart failure
- Myocardial infarction
- Bradycardia (slow heart rate prolongs repolarization)
- Heart block
- Electrolyte abnormalities (hypomagnesemia, hypokalemia, hypocalcemia)
- Liver failure (cirrhosis) and/or renal failure (GFR ≤ 30ml/min) (QT-prolonging drug(s) may accumulate)

Monitoring:

Abnormal heart rate, palpitations, lightheadedness, dizziness, transient shortness of breath, seizures, fainting, and sudden chest pain.

Management:

Avoid concurrent use of more than one drug that can prolong the QT interval, when possible[3,5,6]

2. Serotonin Syndrome[1,7]

Serotonin syndrome (also referred to as serotonin toxicity) is a potentially life-threatening condition that results from excessive serotonin levels within the central nervous system (CNS). Hospice and palliative care patients are frequently prescribed combinations of serotonergic drugs, placing them at high risk.

Symptoms typically develop rapidly, with **most occurring within 2-24 hours of an increase in dose or addition of a serotonergic drug.** Serotonin syndrome is often difficult to recognize in its early stages as symptoms are attributed to the patient's condition or complications of their illness.

Common medication culprits:

- Antidepressants - SSRIs (e.g., citalopram, fluoxetine), TCAs (e.g., amitriptyline), MAOIs (e.g., phenelzine), SNRIs (e.g., venlafaxine, duloxetine)
- Antipsychotics (i.e., olanzapine)
- Opioids (e.g., fentanyl, meperidine, tramadol)
- Others - Trazodone, metoclopramide, ondansetron, dextromethorphan

Monitoring:

Hyperthermia, hypertension, myoclonus, rigidity, and mental status changes. This usually occurs with the first couple of doses of a new offending medication or if a dosage is increased.

Management:

If serotonin syndrome is suspected, stop serotonergic drugs immediately. Supportive care includes:

- Intravenous fluids for dehydration and fever
- β-blockers such as metoprolol to reverse autonomic and neurological symptoms
- Benzodiazepines such as lorazepam or diazepam to decrease agitation, myoclonus, and muscle stiffness
- Hyperthermic patients (temp >105°F) require aggressive supportive care including intravenous sedation, paralysis and breathing support

3. CYP450 Enzyme System

Located in the liver, the cytochrome P450 (CYP450) enzyme system consists of several isoenzymes (1A2, 2C8, 2C9, 2C19, 2D6, 3A4) designated for medication metabolism. Medications affected by one or more of these enzymes are called **substrates**. Medications that slow metabolism of substrates are called **inhibitors** and those that speed up metabolism are called **inducers**.

Recognize that many palliative medications, including QT-prolonging medications, are metabolized by CYP450. It's important to identify them as well as the medications that may inhibit or induce them.[5,8] The Indiana University School of Medicine maintains an interactive CYP450 drug interaction table that may be perused for review or searched for specific medications.[8,9]

Common substrates encountered in hospice:

- Amiodarone (Cordarone®)
- Amitriptyline (Elavil®)
- Donepezil (Aricept®)
- Escitalopram (Lexapro®)
- Methadone
- Mirtazapine (Remeron®)
- Naproxen (Naprosyn®)
- Olanzapine (Zyprexa®)
- Omeprazole (Prilosec®)
- Ondansetron (Zofran®)
- Sertraline (Zoloft®)
- Venlafaxine (Tegretol®
- Verapamil (Calan®)
- Vortioxetine (Trintellex®)
- Warfarin (Coumadin®, Jantoven®)

Inhibitors:

- Azole antifungals (e.g., fluconazole (Diflucan®))
- Cannabidiol (CBD)
- Grapefruit juice
- Ranolazine (Ranexa®)

Inducers:

- Carbamazepine (Tegretol®)
- Phenobarbital
- Phenytoin (Dilantin®)
- St. John's Wort

4. Warfarin (Coumadin®, Jantoven®)

Warfarin is an oral anticoagulant indicated for several thrombotic conditions, including DVT and PE treatment and prophylaxis, post-MI, prosthetic heart valves, atrial fibrillation, and post hip/knee replacement. It is an inexpensive medication, but carries a high risk of adverse effects (bleeding, bruising) and drug-drug and drug-food interactions. Additionally, warfarin has a narrow therapeutic index, requiring lab monitoring (INR) until a stable dose is achieved. It is also important to maintain a stable diet. Terminally ill patients may have frequent changes to medications, and diet may be erratic, both of which may complicate the use of this medication.

Significant interactions include, but are not limited to:[10]

- Alcohol consumption
- Tobacco use
- Erratic diet - Vitamin K decreases the effect of warfarin, and it is found in many foods
- NSAIDS (e.g., ibuprofen, aspirin)
- Warfarin is a CYP450 substrate of isoenzymes 2C9, 2C19, 1A2, 3A4
    - Inhibitors of one or more of the above isoenzymes: amiodarone, amlodipine (Norvasc®), cannabidiol (CBD), ciprofloxacin (Cipro®), citalopram (Celexa®), diltiazem (Cardizem®), fluconazole (Diflucan®), esomeprazole (Nexium®), famotidine (Pepcid®), fluoxetine (Prozac®), lansoprazole (Prevacid®), omeprazole (Prilosec®), oxcarbazepine (Trileptal®), ranolazine (Ranexa®), sulfamethoxazole (found in Bactrim®), valproic acid (Depakene®), certain antiretrovirals, grapefruit, garlic supplements
    - Inducers of one or more of the above isoenzymes: carbamazepine (Tegretol®), oxcarbazepine (Trileptal®), phenobarbital, phenytoin (Dilantin®), St. John's Wort, certain antiretrovirals, garlic supplements

Monitoring:

Indications of a patient administered too much warfarin (INR too high) include bleeding from the gums, unexplained bruises or bruises that get larger, blood in the urine or stool, nosebleed that is not easily stopped, and coughing up or vomiting blood.

Indications of too little warfarin (INR too low) may include pain or swelling of the leg or arm, skin that is red or warm to the touch on your arm or leg, shortness of breath or difficulty breathing, chest pain and unexplained fever.

Management:

Avoid medications that interact with warfarin, when possible. If warfarin and the interacting medication must be continued, adjust the warfarin dose accordingly and monitor the INR more frequently until stabilized. Consider replacing warfarin with anticoagulants with fewer adverse effects and no lab monitoring such as a low molecular weight heparin (LMWH) (e.g., enoxaparin) or a direct oral anticoagulant (DOAC) (e.g., apixaban) where clinically appropriate and financially feasible.

DOCUMENTATION OF ASSESSMENTS & OUTCOMES

Equally important when evaluating a patient's conditions, medications and social habits for potential interactions is documenting your assessment and patient communications with interdisciplinary team members in the patient record. This documentation serves not only as a historical record but as a prospective tool for fellow team members to support monitoring for outcomes and can prevent duplicate evaluation efforts in your absence.

CASE ASSESSMENT & RECOMMENDATIONS

The hospice team caring for TS has managed his medication regimen well, maintaining medications that provide him comfort and deprescribing those no longer beneficial. With only necessary medication, he is less prone to drug interactions. However, adding a medication to manage oral thrush still prompts proper review.

Oral thrush therapies include topical antifungals including clotrimazole troche (Mycelex®) and nystatin (Mycostatin®) suspension, and oral antifungals, typically -azole antifungals like fluconazole (Diflucan®). Topical therapies may be problematic in patients unable to orally manipulate troches or suspension effectively or those with adherence concerns as these products require frequent administration throughout the day. Systemic -azole antifungals may be preferred in these cases, but may be more costly and introduce significant drug-drug interactions, including methadone that manages pain for TS.

Recommendation:

- Clotrimazole troches; one 10 mg troche dissolved in the mouth five times daily for 7-14 days

For more on drug interactions, consider review of these prior cases on related topics:

- Polypharmacy Management
- Serotonin Syndrome Case Study
- Drug-induced QT Prolongation: A Review
- Methadone Conversion: Revisiting a Prior Case
- Oropharyngeal and Esophageal Candidiasis: A Refresher

REFERENCES:

1. Clinical Resource, Drug Interactions: A Practical Approach. Pharmacist's Letter/Prescriber's Letter. February 2017.

2. Berul CI. Acquired long QT syndrome: Definitions, causes, and pathophysiology. In: UpToDate. Asirvatham S, et al, ed. Waltham, MA: UpToDate, Inc. Updated Jan 13, 2020.

3. Dave J. Torsade de Pointes. In: Medscape Drugs & Diseases – Cardiology. Updated January 31, 2017. Article link

4. CredibleMeds®. Resources for HealthCare Professionals. Accessed November 1, 2020. Site link

5. Thompson JL, Crossman RR. Drug-induced QT prolongation. U.S. Pharmacist. February 20, 2007. Article link

6. Miranda DG, McMain CL, Smith AJ. Medication-Induced QT-Interval Prolongation and Torsades de Pointes. U.S. Pharmacist. February 18, 2011. Article link

7. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2021.

8. Clinical Resource, Cytochrome P450 (CYP) Drug Interactions. Pharmacist's Letter/Prescriber's Letter. June 2020.

9. Indiana University School of Medicine. Department of Medicine. Clinical Pharmacology. Flockhart Cytochrome P450 Drug Interaction Table. Site Link

10. Clinical Resource, Comparison of Oral Anticoagulants. Pharmacist's Letter/Prescriber's Letter. December 2019.