Medication Interactions

Introduction

Opioid use disorder (OUD) is highly comorbid with medical illness and other psychiatric conditions. Most of your patients on medications for OUD (MOUD) will also be taking other medications (Du CX et al, *Fam Pract* 2022;39(2):234–240). MOUDs generally play well with other medications, but there are some important interactions to be aware of. Here is a summary of some important med-med interactions to be wary of when prescribing MOUDs.

Central Nervous System (CNS) Depression

The CNS depressant effects of buprenorphine and methadone can be compounded when combined with other sedating medications. Two classes of commonly prescribed medications warrant particular caution (but also be careful with alcohol, barbiturates, and other CNS depressants):

- *Benzodiazepines:* These can have powerful CNS depressant effects, including respiratory suppression, which are additive with those of opioids. Benzo prescriptions are associated with an increased risk of opioid overdose death (Park T et al, *Addiction* 2020;115(5):924–932) and generally should be used only with great caution in those taking an MOUD.
- *Gabapentinoids:* Gabapentin and pregabalin are not particularly dangerous on their own but have increasingly been implicated in opioid overdose deaths in postmortem studies (Mattson CL et al, *Morb Mortal Wkly Rep* 2022;71(19):664–666). While they are almost certainly safer to prescribe than benzos, we recommend caution when combining them with buprenorphine or methadone, especially for those continuing to use illicit opioids.

P450 Interactions

Buprenorphine and methadone are primarily metabolized by CYP3A4, with smaller contributions from other P450 enzyme subsystems. The key is to look out for major inducers and inhibitors, which can affect serum levels. Here are the big ones to know:

- *Inducers:* These lower the serum concentration of buprenorphine and methadone, meaning patients may require higher than expected doses or a dose adjustment when the offending agent is discontinued. If the patient is already on an MOUD and an inducer is started, they may have breakthrough opioid cravings or withdrawal symptoms.
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Rifampin
  - St. John's wort
- *Inhibitors:* These raise the serum concentration of buprenorphine and methadone, meaning patients may require less medication than usual. If the patient is already on an MOUD and an inhibitor is started, they may get sedated. Many antifungals, many antivirals, and some antibacterial agents are strong CYP3A4 inhibitors. As this list is not comprehensive, we recommend utilizing a medication interaction checker such as Micromedex when a new medication is started.
  - Clarithromycin, erythromycin
  - Diltiazem, verapamil
  - Fluvoxamine
  - Grapefruit juice
  - Nefazodone: atypical antidepressant
  - Azole antifungals (itraconazole, fluconazole, ketoconazole, etc)
  - Many antiretroviral medications (atazanavir, delavirdine, indinavir, ritonavir, etc)

Cardiac Issues

Methadone is a well-known QT-prolonging medication. Buprenorphine can prolong the QT interval as well, though to a lesser extent. Perhaps surprisingly, injectable naltrexone is associated with prolonged QT and cardiac arrhythmias as well (Raji MA et al, *Am J Med* 2022;135(7):864–870). Use caution when prescribing an MOUD to patients who have preexisting heart disease or are receiving other QT-prolonging agents such as:

- Many antiarrhythmics (always double-check these)
- Citalopram and escitalopram
- Donepezil
- Pimozide
- IV haloperidol
- IV ondansetron
- Low-potency first-generation antipsychotics
- Azole antifungals (see above)
- Fluoroquinolones (end in "-floxacin": levofloxacin, ciprofloxacin, etc)
- Macrolides (end in "-mycin": erythromycin, clarithromycin, etc)
- VMAT2 inhibitors