UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

August 13, 2021 Vol. 1, No. 20

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Suggested Topic: Drug Interactions with Medical Cannabis

Background:

Cannabis is becoming more widely available to patients given changes in state-level policies surrounding use for medical or recreational purposes. Federally, cannabis is still a Schedule I drug, which makes clinical research extremely challenging. In PA, medical cannabis may be dispensed and administered as pill, oil, topical forms (gels/creams/ointments), tinctures, or liquid for consumption or vaporization if a patient has one of the approved indications (2016 Act 16). At UPMC, a policy exists at PUH-SHY surrounding inpatient medical cannabis use which can be found here: SHY/PUH Policy CP-75 Medical Cannabis during Hospitalization
The major cannabinoids are: cannabidiol (CBD)- non-psychoactive, and tetrahydrocannabinol (THC)- psychoactive. Different combinations of these active cannabinoids are utilized to help mitigate symptoms. This issue of the Tablet is not intended to explore the therapeutic pharmacology, formulations, indications, or evidence surrounding medical cannabis use.

Importance:

We see medical cannabis used by our patients to mitigate symptoms such as nausea, anorexia, insomnia, and pain. It is important for palliative care clinicians to be aware of potential drug-drug interactions with cannabis, specifically the therapeutic cannabinoid, CBD.

The Literature:

J Gen Intern Med. 2021 Jul; 36(7):2074-2084.
Cannabidiol Interactions with Medications, Illicit Substances, and Alcohol: A Comprehensive Review
Literature Review that examined interactions with cannabidiol (CBD) specifically

Background:
- CBD is extensively metabolized by the liver: CYP3A4 and CYP2C19
- CBD inhibits CYP2C19, CYP2D6, and CYP2C9 and *may* inhibit members of the CYP3 family
- Strong inhibitors or strong inducers of CYP3A4 may alter levels of CBD
    - Inhibitors: protease inhibitors, azole antifungals, macrolides, H2 receptor antagonists
        - May increase CBD concentrations
    - Inducers: anticonvulsants, rifampicin, St. John's wort
        - May decrease CBD concentrations
- CBD may increase levels of cyclosporine, sildenafil, antihistamines, haloperidol, antiretrovirals, atorvastatin and simvastatin (not well studied… yet)
- CBD main receptors: CB1 and CB2 are in the central nervous system and peripheral nervous system respectively
- CBD binds to many different receptors that are involved with its mechanism (too much to discuss in detail for this overview)

Will highlight pertinent medications seen in our clinical practice below:
Anticonvulsants
- Interactions through several mechanisms
- Increase in liver enzymes when valproate was administered concomitantly with CBD, no relevant effect on valproate exposure seen
- CBD reduced anticonvulsant properties of chlordiazepoxide, clonazepam
- Of note, CBD has its own seizure-reducing efficacy based on some evidence and could potentially increase the activity of some anticonvulsants:
    - Phenytoin, phenobarbital, topiramate, oxcarbazepine, pregabalin, tiagabine, gabapentin
- No proven interactions with lacosamide and lamotrigine, although this cannot be fully excluded

Antidepressants
- Interactions thought to be through CBD's inhibition of CYP2D6
- Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants serum concentrations may be increased as they are metabolized by 2D6 and patients may be at risk for increased ADE and/or increased efficacy at lower doses

Opioids
- Co-administration of CBD and fentanyl was well tolerated in a double-blind, placebo-controlled trial
- Inhibitory action of CBD at CYP2D6 could potentially reduce active metabolites of codeine, oxycodone, hydrocodone, and tramadol but no studies have been done to test this
- Methadone may have increased serum concentrations with coadministration of CBD; this has not been tested

Warfarin
- CBD may increase INR (case study), reduction in warfarin dose may be necessary

Cyclosporine/Tacrolimus
- CBD may increase both cyclosporine and tacrolimus levels, increasing risk for toxic ADE

Acetaminophen
- Co-administration may result in liver injury (animal study, only); CBD is also suggested to be reduced in setting of hepatic impairment

Alcohol
- CBD may be hepato- and neuro-protective?!
- Co-administration potentiates impairments of motor and psychomotor performances but may make one hyperaware of their intoxication and deficits

Bottom Line:

- CBD may interact with many medications, given its affinity for numerous receptor targets and inhibition of CYP enzymes
- There are still a lot of unknowns, given the limited clinical research capabilities
- More research needs to be done to further characterize and describe these interactions in a clinical setting
- This paper was very detailed and it is easy to get caught in the weeds of the PK/PD of CBD (unless you are a researcher than the weeds are the perfect place to be)
- Recommend starting low and going slow with systemic cannabis administration (ie. oral or inhaled formulations), monitoring for efficacy and safety outcomes.
- It's important to be aware of all medications patients take. Dose adjustments of other medications may be necessary depending on administration route, dosing, and frequency.

CLINICAL PEARL: CBD may be involved in numerous drug-drug interactions. Further research needs to be done to explore clinical implications of these potential interactions.