A Review of Potential Drug-Drug Interactions involving Medical Cannabis and Potentially Inappropriate Medications in Older Adults

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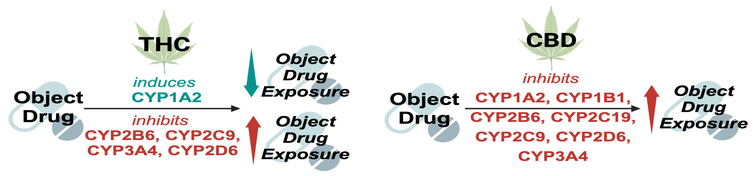
Introduction

- The legalization of medical cannabis (MC) in the United States has resulted in a significant increase in its use among adults over 65 years old over the past two decades
- Despite its growing popularity, few studies have assessed the potential for drug-drug interactions (DDIs) involving MC and potentially inappropriate medications (PIMs) in older adults (MC-PIM DDIs)
- There is a need for an updated review of MC-PIM DDIs given the recently updated 2023 Beers Criteria and advances in MC pharmacokinetic and pharmacodynamic (PK/PD) research
- This study aims to establish a comprehensive list of potential DDIs between PIMs and medical cannabis in the population of older adults, based on existing PK/PD information

Methods

- We conducted an assessment of potential MC-PIM DDIs in older adults (age > 65 years old)
- PIMs were defined using the American Geriatric Society (AGS) 2023 Beers Criteria
- MC-PIM DDIs were systematically assessed using Clinical Pharmacology, FDA package inserts, and literature review

Figure 1: Enzyme targets that may be affected by THC and CBD and mechanism for potential drug-drug interactions



Results

- The review and analysis presented indicate significant pharmacological interactions between medical cannabis and various medications listed in the AGS 2023 Beers Criteria
- These medications span several categories, including antihistamines, cardiovascular drugs, CNS agents, endocrine drugs, gastrointestinal medications, and pain medications
- The interactions generally arise from the ability of THC and CBD to inhibit or induce key CYP450 enzymes, such as CYP2D6, CYP3A4, CYP2C9, and CYP2C19, thus altering the metabolism and effects of concomitant medications

Tables 1 & 2: Potential drug-drug interactions of medical cannabis and potentially inappropriate medications in older adults, per the 2023 American Geriatrics Society Beers Criteria®

Object drug	CBD Effects on Object Drug	THC Effects on Object Drug	Responsible Enzyme(s)/ Protein	Clinical implications
Barbiturates				Physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages
Phenobarbital	↑	↕	2C9, 2C19	
Benzodiazepines				Sedation, respiratory depression, coma, and death; physical dependence; cognitive impairment, delirium, falls, fractures, and motor vehicle crashes; abuse, misuse, addiction
Alprazolam	↑	↑	3A4	
Clobazam	↑	↕	3A4, 2B6, 2D6, 2C19, 2C9	
Diazepam	↑	↑	3A4, 2C19	
Midazolam	↑	↑	3A4	
Triazolam	↑	↑	3A4	
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics (“Z-drugs”)				Delirium, falls, fractures, increased emergency room visits/hospitalizations, and motor vehicle crashes
Eszopiclone	↑	↑	3A4	
Zaleplon	↑	↑	3A4	
Zolpidem	↑	↕	3A4, 2C9	
Endocrine				Cardiac adverse events; potential risks in men with prostate cancer
Androgens				
Testosterone	↑	↑	3A4	
Estrogens with or without progestins				Carcinogenic potential; heart disease, stroke, blood clots, dementia
Estradiol	↑	↑	3A4	
Sulfonylureas (all, including short/longer-acting)				Cardiovascular events, all-cause mortality, and hypoglycemia
Gliclazide	↑	↕	2C9	
Glimepiride	↑	↕	2C9	
Glipizide	↑	↕	2C9	
Glyburide (Glibenclamide)	↑	↕	2C9, BCRP, BSEP	
Proton-pump inhibitors				C. difficile infection, pneumonia, GI malignancies, bone loss, and fractures
Esomeprazole	↑	↑	3A4, 2C19	
Lansoprazole	↑	↑	3A4, 2C19	
Omeprazole	↑	↕	2C9, 2C19, 3A4	
Pantoprazole	↑	↕	2C9, 3A4, 2C19	
Metoclopramide	↑	↑	2D6	Extrapyramidal effects, including tardive dyskinesia
Non-COX-2-selective NSAIDs, oral				GI bleeding or peptic ulcer disease in high-risk groups; hypertension and kidney injury
Diclofenac	↑	↕	2C9,3A4	
Flurbiprofen	↑	↕	2C9, UGT2B7	
Ibuprofen	↑	↕	2C9, UGT1A9, UGT2B7	
Meloxicam	↑	↕	2C9	
Nabumetone	↑	↓	1A2	
Naproxen	↑	↕	1A2, 2C9, UGT2B7	
Piroxicam	↑	↕	2C9	
Indomethacin	↑	↕	2C9	
Meperidine	↑	↑	2B6, 3A4	GI bleeding/peptic ulcer disease and acute kidney injury; adverse CNS effects; Neurotoxicity, including delirium
Skeletal muscle relaxants				Anticholinergic adverse effects, sedation, and increased risk of fractures
Carisoprodol	↑	↑	2C19	
Cyclobenzaprine	↑	↕	1A2,3A4	

Object drug	CBD Effects on Object Drug	THC Effects on Object Drug	Responsible Enzyme(s)/ Protein	Clinical implications
Warfarin	↑	↕	1A2, 2C9, 2C19	Major bleeding (particularly intracranial bleeding)
Rivaroxaban	↑	↑	3A4	Major bleeding and GI bleeding
Ticagrelor	↑	↑	3A4	Major bleeding
Central alpha-agonists, Clonidine	↑	↑	2D6	CNS effects, bradycardia, and orthostatic hypotension
Nifedipine, immediate release	↑	↑	3A4	Hypotension, risk of precipitating myocardial ischemia
Dipyridamole	↑		BCRP	Orthostatic hypotension
Dronedarone	↑	↑	2D6, 3A4	Worse outcomes in people who have permanent atrial fibrillation or severe or recently decompensated heart failure
Digoxin	↑		BSEP	Toxicity
Amiodarone	↑	↑	2D6, 3A4	Greater toxicities than other antiarrhythmics used in atrial fibrillation
First-generation antihistamines				Anticholinergic effects or toxicity, confusion, dry mouth, constipation, falls, delirium, and dementia
Chlorpheniramine	↑	↑	2D6	
Diphenhydramine	↑	↑	2D6	
Hydroxyzine	↑	↑	3A4	
Promethazine	↑	↑	2D6	
Central nervous system				Highly anticholinergic, sedating, and cause orthostatic hypotension
Antidepressants with strong anticholinergic activity				
Amitriptyline	↑	↕	1A2, 2C9, 2D6, 3A4, 2C19	
Clomipramine	↑	↕	1A2, 2D6	
Desipramine	↑	↑	2D6	
Doxepin	↑	↕	2C9, 2D6, 2C19, 1A2	
Imipramine	↑	↕	1A2, 2D6, 2C19	
Nortriptyline	↑	↑	2D6, 3A4	
Paroxetine	↑	↑	2D6	
Typical antipsychotics				Stroke, cognitive decline, and mortality in persons with dementia
Chlorpromazine	↑	↕	2D6, 3A4, 1A2	
Haloperidol	↑	↕	1A2, 2D6, 3A4, UGT1A9	
Perphenazine	↑	↑	2D6	
Atypical antipsychotics				
Aripiprazole	↑	↑	2D6, 3A4	
Brexpiprazole	↑	↑	2D6, 3A4	
Cariprazine	↑	↑	2D6, 3A4	
Clozapine	↑	↕	1A2, 2D6, 3A4	
Olanzapine	↑	↕	1A2, 2D6	
Pimavanserin	↑	↑	2D6, 3A4	
Quetiapine	↑	↑	3A4	
Risperidone	↑	↑	2D6, 3A4	
Ziprasidone	↑	↕	3A4, 1A2	

Change in Object Drug Exposure: ↑ Increase | ↓ Decrease | ↕ Conflicting

Discussion

- The potential clinical implications of these interactions include heightened risk of adverse drug events (ADEs) such as sedation, confusion, orthostatic hypotension, bleeding, cognitive impairment, cardiovascular issues, and gastrointestinal problems
- Given the vulnerable characteristics of the older population, such as polypharmacy, age-related physiological changes, and higher susceptibility to adverse effects, there is a clear need for vigilant medication management and patient monitoring

Conclusions and Key Takeaways

- MC has the potential to interact with multiple classes of PIMs in older adults
- The following clinical suggestions should be emphasized when prescribing MC with PIMs:
  A. Conduct medication reviews to identify potential DDIs and adverse drug effects
  B. Evaluate fall risk, neuropsychiatric conditions, and cardiovascular disease
  C. Titrate doses of THC/CBD gradually
  D. Deprescribe MC and PIMs when possible

References

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Disclosures and Acknowledgements

FM, SJ, AG, and EM were supported by a grant from the Consortium for Medical Marijuana Clinical Outcomes Research, which receives funding from the State of Florida appropriations, for this work.