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Opioid Prescribing and the Opioid Crisis in the Lower Extremity

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Introduction

The phenomenon of pain is the result of unpleasant and subjective sensation resulting from a noxious sensory stimulus. The foot and ankle physician is no stranger to the difficulties in achieving optimal pain therapy. All clinical providers must develop analgesic regimens to treat patients with acute, chronic, and postoperative pain [1]. The topic of pain management remains a minor component of the formal education and training of residents and physicians in the United States. Erroneous attitudes concerning acute and chronic pain management, in addition to reservations about the legal aspects of pain management, often translate into a "fear of the unknown" when it comes to narcotic prescription [2]. On an average day in the United States more than 650,000 opioid prescriptions are dispensed [3]. Further, the United States accounts for 4.6% of the world's population yet it is estimated that the United States consumes 80 percent of the global opioid supply [4]. The United States is in the grips of an Opioid Crisis described by staggering data. Of the 20.5 million Americans 12 or older that had a substance use disorder in 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [5].

Foot and ankle physicians during their role of patient pain management frequently prescribe of opioids; physicians have an ethical obligation to prescribe responsibly yet cautiously to diminish the potential for opioid diversion and to help minimize the growth of the current epidemic in opioid abuse. Through alterations in the attitudes of patients and physicians, the foot and ankle specialist can manage the pain of the patient while minimizing diversion potential through careful procedural techniques, non-steroidal anti-inflammatory drug use, and limited opioid prescriptions of appropriate quantities when deemed necessary. In order to manage their patients' pain after invasive lower extremity procedures, every practicing foot and ankle specialist must prescribe medication on occasion. Many of these analgesic medications are associated with a high likelihood of physical dependence, as well as a relatively high risk of addiction. It is critical that clinical providers understand the underlying issues of how these medications work and how they can be abused, as well as exercise sound clinical judgment in identifying patients who might possibly have or develop a physical or psychological dependence on these drugs after only five days of therapy. Because there exists a dilemma for the clinician with regarding balancing patient treatment with opioid and avoiding contributing to the opioid crisis, this review focuses on the prescribing of opioid analgesics to treat lower-extremity pain. The selection of an appropriate opioid agent and prescribing strategies are introduced. Then, to enrich the lower extremity physician's body opioid drug-drug interactions are presented to help prevent deadly implications. Finally, a commentary and discussion centered on the movement to mandate opioid prescription taxes will be presented.

Prescribing Opioid Strategies in the Lower Extremity Practice

Analgesic opioid therapy has been the cornerstone of the pharmacologic management of acute and chronic pain. Ideally, opioid analgesic is prescribed by balancing the beneficial and adverse effects. Although often overlooked as a source of opioid medications, podiatric and orthopedic surgical intervention procedures are often painful

during the post-operative period and therefore these specialists are frequent opioid prescribers. Ringwalt et al, report accentuates this by their findings centered on medical specialty opioid prescribing for non-chronic, non-cancer pain [6]. They reviewed 1.28 million filled prescriptions for an opioid analgesic over a one-year time frame [6]. They concluded that general practitioner/family medicine specialists and internists were least likely to prescribe opioids, while orthopedists were most likely to prescribe opioids [6]. While there is currently no direct evidence, a contribution to non-medical opioid misuse is presumed to be a result of normal prescribing for orthopedic surgical interventions.

Opioid analgesics are classified as agonist or antagonist drugs depending on their ability to bind or block opioid receptors [1,7]. Opioids each produce a wide spectrum of pharmacologic effects, including analgesia, dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, urinary retention, histamine release, and physical dependence [1]. The podiatric physician must remem-

ber that comfort is the ultimate goal when using any medication, including opioids, to manage pain. Before clinicians consider an opioid analgesic, they need to ensure that a complete psychosocial and physical evaluation of the patient has been performed. Opioid therapy should be prescribed appropriately to avoid undertreating patients with painful symptoms.

Opioid selection is based on patient-specific factors, such as age and renal function. In the setting of acute pain, some podiatric clinicians become competent in the prescribing and use of a few opioid analgesics. Although no opioid seems to be superior in relieving pain, certain products are clearly inferior because of increased risks of toxic effects [1,8]. In some circumstances; pain control is inadequate despite dosage increases. MacPherson [1,9] reviewed the concept of opioid rotation. This method is the replacement of the current opioid regimen with another. Analgesic equivalence is the central theme when considering opioid substitution [1,9]. Mercadante [1,10]. defines the concept of opioid rotation as the substitution of another opioid for a previous one to obtain a more favorable response. Two types of opioid rotation strategies have been used: a change in opioid products or a change in the route of administration. Morphine-equivalent tables have been developed, and their purpose is to present information related to equianalgesic doses of various opioid agents compared with morphine to assist clinicians with rotating opioid products. A table of opioid equianalgesic doses is presented here as (Table 1).

Opioid Products	Oral Route	IV/SC/IM Routes
Morphine	30 mg	10 mg
Codeine	130 mg	75 mg
Hydromorphone	7.5 mg	1.5 mg
Methadone	5-15 mg	2,5mg-10 mg
Meperidine	300 mg	75 mg
Levorphanol	4 mg	2 mg
Oxymorphone	10 mg	1 mg
Pentazocine	50 mg	30 mg
Hydrocodone	20 mg	N/A
Oxycodone	20 mg	N/A
Buprenorphine	N/A	0.3 mg-0.4 mg
Butorphanol	N/A	2 mg
Fentanyl	N/A	0.1 mg
Nalbuphine	N/A	10 mg

Table 1: Opioid Equivalency.

A final element of opioid analgesic therapy that physicians must consider is the route of administration. Various methods of drug delivery have been used to treat patients in pain.

Institute for Clinical Systems Improvement published an acute pain assessment and appropriate opioid prescribing protocol in 2014. The Foot and Ankle physician may find the following clinical points essential when prescribing opioids for acute pain [11]. Providers should avoid prescribing more than 3 days or 20 tablets or capsules to a patient [11]. Select the lowest dose and the shortest acting opioid product. Consider that tramadol is an atypical opioid and should be managed appropriately [11]. Never prescribe long-acting/extended release opioid for acute pain. Exercise caution when prescribing opioids to the elderly patient [11]. Schedule the patient to follow up within 3-5 days. Share decision-making and review responsible use, driving, work, storage and disposal with patient [11].

Finally, published clinical-based evidence has described the effects of employing local anesthetic products to reduce postoperative pain and reduce the need for opioid analgesics [12-14]. Many treatments are available to manage pain. Some non-opioid therapies are likely to be as effective as opioids, or even more so and potentially carry lower risk when used appropriately. Any meaningful effort to improve pain management will require a basic culture shift in the nation's approach to mandating pain-related education for all health professionals who provide care to people with pain.

Opioid Drug-Drug Interactions

As a drug class, opioids are associated with a narrow therapeutic index, wide interindividual variability in response and potentially life-threatening toxicity. It is certain that the podiatric physician cannot be expected to memorize the staggering number of pharmaceuticals available and the equally daunting potential for drug interactions. However, prescribers should recognize that patients often come to them medicated with scores of drugs acquired from multiple sources. A meticulous drug history should include examination of the patient's prescribed medications as well as over-the-counter drugs, herbal supplements, illicit drugs, cigarettes, and alcohol consumptions. General principles of drug interactions should be understood and the major risks for interactions should be appreciated for the principal drug classes prescribed. There are a number of mechanisms by which drugs interact with each other, and most of them can be divided into two general categories: pharmacokinetic and pharmacodynamics interactions. With pharmacokinetic drug interactions, one drug affects the absorption, distribution, metabolism, or excretion of another. When pharmacodynamic drug interactions occur, two drugs have additive or antagonistic pharmacologic effects. Either type of drug interaction can result in adverse effects in some individuals [1].

The primary mechanisms of drug interactions include effects of drugs on hepatic metabolism of pharmaceuticals including effects on Cytochrome P450 (CYP) enzymes or effects on glucuronidation, medication effects on the function of the drug transporter, P-glycoprotein, and effects on absorption of drugs [15-17]. Most opioid medications are metabolized by one or more of the CYP450 isozymes, and this process typically results in the generation of multiple metabolites. In addition, other prescription medications, Over-The-Counter (OTC) medications, "herbals," dietary supplements, and smoking can inhibit or induce the activity

of CYP450 enzymes involved in the metabolic pathways of opioid medications. Some important preventable drug interactions are attributable to their effects on drug-metabolizing enzymes, resulting in either reduced activity of the enzyme (enzyme inhibition) or increased activity of the enzyme (enzyme induction). The major group of enzymes in the liver responsible for metabolizing drugs can be isolated in a subcellular fraction termed microsomes. Cytochrome P450 is a superfamily of enzymes that are the terminal oxidases of this oxidation system. Cytochrome means colored cells; these enzymes contain iron, giving the liver its red color. The name P450 comes from the observation that the enzyme absorbs a very characteristic wavelength (450 nm) of ultraviolet light when it is exposed to carbon monoxide. These enzymes are named according to families that are defined by the similarity of their amino acid sequence. The nomenclature of each cytochrome isoenzyme follows some simple rules.[1] Using CYP3A4 as an example, the root of its name is "CYP." Its family is noted with the number "3," and its subfamily is represented with the letter "A." Its gene is denoted with the last number in the series, "4." [1,15-17].

Codeine has a high potential for drug interactions since it is metabolized by both the CYP450 2D6 and 3A isoenzymes. Codeine confers most of its analgesic effects through the formation of its metabolites.

Rifampin is a CYP450 inducers have similar clinical consequences to CYP2D6 inhibitors when co-administered with codeine. The induction of CYP3A by rifampin will enhance codeine's conversion to the inactive metabolite, norcodeine and prevent codeine's conversion to morphine. There are minimal pharmacokinetic changes between morphine and CYP3A inducers and CYP3A inhibitors likely clinically inconsequential; however, still monitor for possible toxicity.

Oxycodone is metabolized in the liver by CYP3A (approximately 80%) to the inactive metabolite noroxycodone, and to a lesser extent by CYP2D6 (less than 10%) to the active metabolite oxymorphone. Numerous interactions between oxycodone and CYP3A inhibitors and inducers have been reported. Rifampin has been shown to markedly reduce oxycodone plasma levels. In controlled trials with healthy volunteers, the CYP3A inhibitors telithromycin, itraconazole, ketoconazole, miconazole, voriconazole, ritonavir, lopinavir, and grapefruit juice all

substantially increased oxycodone exposure, generally resulting in increased opioid effects. Voriconazole can produce a 4-fold increase in oxycodone plasma concentrations. Hydrocodone is a prodrug opioid, and the parent compound is a relatively weak μ-receptor agonist. Hydrocodone is metabolized into its active moiety, hydromorphone, by CYP2D6. Hydromorphone is unlikely to be associated with pharmacokinetic drug-drug interactions based on its metabolism; because hydromorphone is metabolized by phase II metabolism. Inhibition of tramadol metabolism either by CYP2D6 or CYP3A inhibition may increase the risk of serious adverse effects to include serotonin syndrome or seizures. There have been a number of cases of serotonin syndrome following the use of serotonergic analgesics such as meperidine, tramadol, and Tapentadol with Selective Serotonin Reuptake Inhibitors (SSRIs) or selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). Limited evidence suggests that fentantyl may also exhibit additive serotonergic effects with other serotonergic drugs. For this review, observed pharmacokinetic and pharmacodynamic changes resulting from the interaction with opioids and frequently prescribed medications by foot and ankle physicians (Table 2).

Prescribed Opioids	Substance Causing Drug Interactions	Explanation or Effect of Drug Interaction
Opioid Analgesic Class	Sedatives Barbituates - Anxiolytics-Benzodiazepines	Profound sedation and respiratory depression may occur with any class of drug with sedative effect
Afentanil	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-	Excessive opioid Effects by causing reduced elimination of opioids
	Fluconazole-Itraconazole-Ketoconazole-Quinupristin	
	Amiodarone- Cimetidine-Cyclosporine-Diltiazem-Dronedarone	Excessive opioid Effects by causing reduced elimination of opioids
	Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	

Codeine	SSRIs Antidepressants Bupropion	Inhibit the prodrug conversion to active morphine derivative; thus decrease and reduce analgesic effects
	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-	Excessive opioid Effects by causing reduced elimination of opioids
	Fluconazole-Itraconazole-Ketoconazole-Quinupristin	
	Amiodarone- Cimetidine-Cyclosporine-Diltiazem-Dronedarone	Excessive opioid Effects by causing reduced elimination of opioids
	Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	
Fentanyl	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-	Excessive opioid Effects by causing reduced elimination of opioids
	Fluconazole-Itraconazole-Ketoconazole-Quinupristin	
	Amiodarone- Cimetidine-Cyclosporine-Diltiazem-Dronedarone	Excessive opioid Effects by causing reduced elimination of opioids
	Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	
Hydrocodone	SSRIs Antidepressants Bupropion	Inhibit the prodrug conversion to active morphine derivative; thus decrease and reduce analgesic effects
Morphine	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
Meperidine	MAO Inhibitors Phenelzine (Nardil) Selegiline (Eldepryl)	Mechanism of interaction is unclear, but hypertensive crisis, seizures, coma have been reported with this combination
Oxycodone	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-	Excessive opioid Effects by causing reduced elimination of opioids
	Fluconazole-Itraconazole-Ketoconazole-Quinupristin	
	Amiodarone- Cimetidine-Cyclosporin-Diltiazem-Dronedarone	Excessive opioid Effects by causing reduced elimination of opioids
	Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	
Sufentanil	Cabamazepine-Oxcarbazepine-Phenytoin-Pyrimidine-Rifampin-HAARTs*	Reduce Analgesic Effects and May Cause Withdrawal Symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-	Excessive opioid Effects by causing reduced elimination of opioids
	Fluconazole-Itraconazole-Ketoconazole-Quinupristin	
	Amiodarone- Cimetidine-Cyclosporin-Diltiazem-Dronedarone	Excessive opioid Effects by causing reduced elimination of opioids
	Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	
Tapentadol	MAO Inhibitors, SSRIs, SNRIs	Contraindicated -Number of cases of Serotonin Syndrome and inhabitation opioid metabolism
Tramadol	MAO Inhibitors, SSRIs, SNRIs, Amitriptyline	Contraindicated -Number of cases of Serotonin Syndrome and inhabitation opioid metabolism
HAARTs: Highly Active Antiretroviral Therapy, **MAO Inhibitors:** Monoamine Oxidase Inhibitors, **SSRIs:** Selective Serotonin Reuptake Inhibitors, **SNRIs:** Selective Serotonin-Norepinephrine Reuptake Inhibitors		

Table 2 Interactions of Opioid Analgesic Drugs Commonly Used in Podiatry Practice.

The table was constructed listing the opioid medications followed by the information concerning drug interactions using the terms: Enzyme inducers, enzyme inhibitors, and outcomes or adverse effects of the co-administration and resulting drug-drug interactions. Enzyme inducers are substances that may increase the elimination of opioids via CYP3A4 metabolism and possibly other pathways. This results in reduced analgesic effects and possible opioid withdrawal symptoms. Enzyme inhibitors may inhibit the elimination of opioids via CYP3A4 metabolism and possibly other pathways. Excessive opioid effects have been reported. Antimicrobials that inhibit CYP3A4 and may inhibit the elimination opioids via CYP3A4 metabolism and possibly other pathways.

The use of herbal remedies has been around for centuries, and their use in both eastern and western societies are well documented. Complementary medicines are widely available at many health food stores, pharmacies, and doctors' offices. The use of dietary supplements and herbal products in the United States has continued through 2018. Numerous herbal supplements are known to cause drug interactions specifically the opioid drug class that can increase the risks associated with surgery and anesthesia as well as pain control [18]. The concomitant use of opioid analgesics with sedative herbs: valerian, kava, and chamomile, may lead to increase central nervous system depression and additive sedation from opioids. The analgesic effect of opioids may be inhibited with the co-administration of ginseng [18]. Plasma concentrations of oxycodone was reduced with the co-administration of St. John's Wort leading to a decrease in analgesic effects [18].

Nearly 40 million US adults still smoke cigarettes, and about 4.7 million middle and high school students use at least one tobacco product, including e-cigarettes. Every day, more than 3,800 youth younger than 18 years smoke their first cigarette [19]. Further the percent of persons aged 12 years and over with any illicit drug use in the past month during 2015 was estimated to be 10.1%. While the percent of persons aged 12 years and over with any nonmedical use of a psychotherapeutic drug in the past month during 2015 was 2.4%. Cigarette smoke, alcohol consumption and co-ingestion of illicit drugs may interact with opioid medications through pharmacokinetic or pharmacodynamics mechanisms [15,17]. Polycyclic aromatic hydrocarbons in tobacco smoke are believed to be responsible for the induction of cytochrome P450, CYP1A1, CYP1A2, and, possibly, CYP2E1[15]. Among its various biological effects, cigarette smoke creates a pharmacokinetic reaction, resulting in drug induction and a change in drug clearance [15,17,18].

Alcohol is pharmacologically classified as a central nervous system depressant. Narcotic pain relievers are prescribed for moderate to severe pain. The combination of opioids and alcohol enhances the sedative effect of both substances, increasing the risk of death from an overdose [15,17].

Alcohol consumption can be a contributing respiratory depression. Alcohol consumption can be a contributing factor in opioid overdose due to additive or factor in opioid overdose due to additive or synergistic respirator. Alcohol is converted by Alcohol Dehyrdogenase (ADH) to acetaldehyde and then converted by aldehyde dehydrogenase Acetaldehyde is converted by Aldehyde Dehydrogenase (ALDH) to acetic acid, then to CO2 and water in the Krebs cycle. Acute ethanol consumption can inhibit CYP3A4, potentiating morphine; conversely chronic ethanol consumption induces CYP3A4, increasing morphine metabolism and reducing effects [15,17]. Benzodiazepines, which are excessively sedating, may cause severe drowsiness in the presence of alcohol. Fatal drug interactions between opioids and benzodiazepines, alcohol, and other sedative-hypnotic drugs have been well published and studied [15].

Given that many health-care providers overlook or are unaware of most drug-to-drug interactions, it is important that the clinician be knowledgeable about the existence of drug interactions with herbal substances, cigarette smoking, and alcohol ingestion. When opioids and social behaviors are combined for other indications, generally by oral administration, dosages must be conservative.

Conclusions

In podiatric practice, drug interactions are not as voluminous as they are in medical practice. This is based on the fact that most drug therapy is short-term and the number of drug classes prescribed is small in comparison. This review offers the health-care provider information regarding potential opioid prescription drug interactions with other drug classes as well as social behaviors. Empowered with this information, clinicians may assist their patients to maximize pharmacologic outcomes by avoiding these reported harmful interactions.

Opioid Prescription Taxes

Historically, in the United States, there has never been much commercial cultivation of the opium and there was no immediate question of opium production, the occasional abusive use of the capsules had already attracted attention during the 1940s. The Narcotics Bureau of the United States was quite unwilling to see the cultivation of the opium poppy extended far and wide over the country, with the potentiality of narcotic evils in its wake. In response, the Federal poppy control bill was passed by both Houses of Congress and was signed by the President on Saturday, December 12, 1942, making it unlawful for any person to produce the opium poppy except under license, and licenses were to be issued only if necessary to supply the medical and scientific needs of the United States for opium or opium products. In most states the Opium Poppy Control Act immediately ended commercial poppy cultivation, but in California it only produced protests and demands that the cultivation be licensed. Under California law any person of good moral character could obtain a state permit to cultivate the opium poppy and continued to grow and cultivate opium poppies. On August 28, 1944 the three judges handed down a unanimous

decision holding the Opium Poppy Control Act constitutional. Soon after, the growers decided not to appeal to the Supreme Court of the United States, thus ended the California "Poppy Rebellion". The real purpose of the law was the exact opposite-not to "promote production of the opium poppy" but to end it. At the time, it was the belief of the United States that the only way to conquer the opium evil was by restricting, and, where necessary, completely abolishing, the cultivation of the opium poppy plant itself. The Opium Poppy control act of 1942 was repealed on October 27, 1970.

No state has enacted a specific tax on prescription painkillers, according to the National Conference of State Legislatures, despite plans being introduced in a dozen states like California, Iowa, and New York, where these state plans stipulated that at least some of the revenue raised would go to fighting addiction. Proposed legislation introduced in Alaska, Tennessee, Minnesota, and other states would or would have created treatment and education programs and funded drug courts. However as reported in March 2018, Kentucky lawmaker are weighing whether to impose a new tax on opioid prescriptions to generate new revenue from the painkillers that helped seed a nationwide addiction crisis. The proposed tax - a 25-cent levy on drug distributors for every dose sent to the state - was approved by the Kentucky House Thursday as part of a broader budget and tax plan. But unlike in other states, where lawmakers aimed to steer the new revenue to addiction treatment and education programs, the Kentucky plan, if enacted, would direct the money to fill budget gaps elsewhere, including boosting funding for the state's public schools [20,21,22].

It is commendable that many states are proposing legislation to generate dollars to treat and battle opioid addiction. The imposition of a tax will certainly affect manufacturers and distributors of opioids. Of course, making certain drugs more expensive will lead to a decrease of production and a resulting decrease in consumption. Many states have now legislated limits on prescription control substances based on day supply or morphine milligram equivalents as well as mandating prescribers to have educational programs centered on opioid prescribing which will impact thus restricting the lawful supply of opioids; influencing prescribing practices; reducing demand and reducing harm as proposed by the Board on Health Sciences Policy; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine. Finally, there exist unanswered centered around taxing opioid prescriptions: (1) how could they prevent the tax from being passed on to consumers? (2)

Would it hurt patients who need pain pills? (3) Could a tax actually reduce the number of overdoses and drug users? It is this author's hope that these questions can be answered quickly and seamlessly so that we as providers do not experience Déjà of the likes of the Opium Poppy control act of 1942.

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