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REVIEW

Pharmacologic Treatment of Opioid Use Disorder: a Review of Pharmacotherapy, Adjuncts, and Toxicity

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Abstract

Opioid use disorder continues to be a significant source of morbidity and mortality in the USA and the world. Pharmacologic treatment with methadone and buprenorphine has been shown to be effective at retaining people in treatment programs, decreasing illicit opioid use, decreasing rates of hepatitis B, and reducing all cause and overdose mortality. Unfortunately, barriers exist in accessing these lifesaving medications: users wishing to start buprenorphine therapy require a waivered provider to prescribe the medication, while some states have no methadone clinics. As such, users looking to wean themselves from opioids or treat their opioid dependence will turn to alternative agents. These agents include using prescription medications, like clonidine or gabapentin, off-label, or over the counter drugs, like loperamide, in supratherapeutic doses. This review provides information on the pharmacology and the toxic effects of pharmacologic agents that are used to treat opioid use disorder. The xenobiotics reviewed in depth include buprenorphine, clonidine, kratom, loperamide, and methadone, with additional information provided on lofexidine, akuamma seeds, kava, and gabapentin.

Keywords Opioid · Withdrawal · Opioid use disorder · Heroin · Buprenorphine · Clonidine · Kratom · Loperamide · Methadone

Abbreviations

AAPCC NPDS	American Association of Poison Control Centers' National Poison Data System
ADHD	Attention-deficit hyperactivity disorder
BUP	Buprenorphine and buprenorphine/naloxone
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CYP	Cytochrome P450
DEA	Drug Enforcement Agency
ECG	Electrocardiogram
EDDP	2-Ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine
FDA	Food and Drug Administration
GABA	γ-Amino butyric acid
hERG	*Human ether-a-go-go-related gene*
I-1	Imidazoline-1
I_{Kr}	Potassium rectifier channel
IV	Intravenous
MAT	Medication-assisted treatment
MME	Morphine milligram equivalents
OUD	Opioid use disorder
QTcF	Fridericia rate-corrected QT
P-gp	P-glycoprotein
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
TdP	Torsades de pointes

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Introduction

Six percent of individuals prescribed opioids continue to use opioids at 1 year [1]. This risk of continued opioid use increases exponentially after 5 days of exposure, contributing to the epidemic of non-medical opioid use, opioid use disorder (OUD), overdose, and deaths. Non-medical opioid use is a well-described gateway to the use of injection opioid use like heroin,

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fueling a persistent rise in opioid overdose death in the USA [2–6]. The recent detection of synthetic opioids (e.g., clandestine fentanyls and designer opioids) in heroin has contributed to a dramatic 70% increase in overdose deaths in 2014–2015 [7]. There are some indications that public health efforts such as provider education and implementation of the prescription monitoring programs have impacted opioid prescribing as the number of opioid prescriptions have decreased from 782 morphine milligram equivalents (MME) per capita in 2010 to 640 MME per capita in 2015; this is still roughly four times the amount distributed in Europe in 2015 [8–11]. Despite efforts to decrease opioid prescribing, deaths attributed to opioid analgesics increased from 16,651 to 22,598 over the same 5 years [12]. Mortality due to non-medical use of opioids remains a serious concern. In 2015, nearly 12.5 million people 12 years of age or older reported using prescription opioids non-medically [13].

Opioid use disorder can be treated with methadone or buprenorphine, often in combination with behavioral therapy. Alternatively, individuals may turn to non-Food and Drug Administration (FDA)-approved medications to manage OUD. For example, a physician may prescribe clonidine to address the physical effects of opioid withdrawal, or a user may consider the use of high doses of loperamide to manage opioid use. Finally, individuals may use herbal supplements like kratom to prevent opioid withdrawal. Each of these therapies for opioid use disorder is associated with unique toxicities that providers should recognize. Although medication-assisted treatment (MAT) of OUD can decrease the incidence of opioid overdose, addiction, and death, access to methadone or buprenorphine is limited due to institutional burdens of establishing OUD treatment centers and legal requirements surrounding the prescribing of buprenorphine. Although recent initiatives to train physicians to prescribe buprenorphine as MAT have seen increasing enrollments, most of these providers are located in major metropolitan areas, restricting access to rural patients. Additionally, the amount of opioids prescribed has decreased every year since 2010 [14]. The decreased availability of prescription opioids for non-medical use may force individuals to use alternative methods to maintain their high, prevent withdrawal, or treat OUD.

In this manuscript, we review the basic pharmacology, application, and toxicology of the various pharmacologic methods of treating OUD. We will focus on treatment options that are available in the USA with the understanding that management of OUD is complicated and treated differently in different countries. Given this complexity, it is not possible to address every treatment option and a preference is made to discuss agents that can produce acute toxicity and that are often illicitly obtained or used off-label to manage withdrawal. As such, naltrexone, a μ-opioid receptor antagonist available as a daily tablet or as a monthly extended release injectable formulation, will not be discussed. Agents will be grouped by those that target the μ-opioid receptor and are considered first-line treatment options (buprenorphine, methadone), central α_2-adrenergic agonists (clonidine, lofexidine), and alternative agents (loperamide, kratom, gabapentin, akuamma, kava).

Mu-Opioid Receptor Agonists

Buprenorphine

Introduction

Buprenorphine and buprenorphine/naloxone (henceforth referred to as BUP) have been indicated for the treatment of opioid dependence since 2002 in the USA. In 2010, a sublingual film formulation was approved for clinical use, providing users with an alternative to the tablet formulation [15]. The use of BUP as MAT for OUD remains highly regulated in the USA; the Drug Addiction Treatment Act (2000) allows physicians to prescribe BUP for 30 patients to manage of opioid use disorder after a series of training activities and competency tests (X-Waiver) [16]. Providers can then petition the Drug Enforcement Agency (DEA) for an increase to 100 patients. After a year of prescribing BUP to 100 patients, a further increase in this limit to 275 patients is permitted [17]. There is also evidence that initiating BUP in the emergency department can increase engagement in addiction treatment and decrease illicit opioid use [18, 19]. Despite relaxed limits on the number of patients treated, access to BUP remains difficult. One report describes 43% of counties in the USA still have no physicians who are X-waivered to prescribe BUP [20]. In adolescents, only 25% of individuals who require treatment for OUD are able to access BUP [21]. This has resulted in a phenomenon of informal treatment of OUD through BUP diversion. Individuals who are in BUP treatment may divert a portion of their prescribed BUP to help treat others without access to a BUP prescriber [22, 23].

Compared to methadone, BUP is administered by the individual in a setting of their choosing, removing the need for daily clinic visits. Patients wishing to initiate BUP maintenance therapy should abstain from opioids for 12 to 48 h or exhibit mild to moderate signs and symptoms of opioid withdrawal measured using the Clinical Opiate Withdrawal Scale (COWS). For reference, a score of 5–12 indicates mild withdrawal, 13–24 moderate withdrawal, 25–36 moderately severe withdrawal, and >36 severe withdrawal [24, 25]. The starting dose is typically 4 to 8 mg, although additional doses can be administered depending on the patient's needs [26].

Pharmacology

Buprenorphine is a highly lipophilic, partial μ-opioid receptor agonist with a long half-life (mean half-life ~37 h) and high binding affinity for the μ-opioid receptor (more than 1000 times that of morphine) [27]. In addition to binding to the μ-opioid receptor, BUP also binds to the κ- and δ-opioid receptors, albeit

with lower affinity [28, 29]. Buprenorphine's activity at the κ-opioid receptor is unclear, with studies reporting both partial agonist and antagonist activity [29–31]. Antagonism of the κ-opioid receptor leads to decreased spinal analgesia, dysphoria, miosis, and diuresis through inhibition of anti-diuretic hormone release [32, 33]. Finally, BUP also binds to the opioid receptor-like receptor (also known as NOP). Stimulation of this receptor blocks the rewarding and antinociceptive actions of morphine [28]. Sublingual bioavailability of BUP is approximately 30%, with rapid absorption producing a peak plasma concentration within 1 h [34, 35]. Buprenorphine is frequently co-formulated with naloxone, a μ-opioid receptor antagonist, which serves as a deterrent to intravenous (IV) abuse of the medication as IV naloxone administration would quickly induce opioid withdrawal. Oral or sublingual administration of naloxone does not induce opioid withdrawal due to the negligible oral bioavailability of naloxone. [35]. Importantly, due to its high binding affinity and ability to displace many full opioid receptor agonists, administration of BUP to individuals actively using opioids can precipitate opioid withdrawal [25]. Buprenorphine is metabolized to norbuprenorphine, its major metabolite, via cytochrome P450 (CYP) 3A4 [27, 35]. Norbuprenorphine is thought to be responsible for the respiratory depressant effects of BUP [36]. Both BUP and norbuprenorphine are glucuronidated and excreted in the feces and urine [35].

Buprenorphine can be administered in a variety of formulations, depending on whether the patient is using BUP for OUD or pain control. Buprenorphine/naloxone combination products that are FDA approved for the treatment of OUD can be found in both sublingual tablet and film formulations. Brand names include Suboxone® (tablet and film, see below for further discussion), Zubsolv® (tablet), Bunavail® (film), and Cassipa® (film). Sublingual BUP tablets (without naloxone) are sold under the brand name Subutex®. Generic versions of sublingual tablet BUP and buprenorphine/naloxone are available. In June 2018, the FDA approved the first generic buprenorphine/naloxone sublingual film for the treatment of OUD with the hope of increasing access to MAT [37].

In addition to treating OUD, BUP is also used in the treatment of pain. Intravenous BUP (Buprenex®) was approved in 1981 for the treatment of moderate to severe pain. Butrans® is a BUP-containing transdermal patch used for around-the-clock pain control. Dosages range from 5 to 20 μg/h. Finally, Belbuca®, a long-acting BUP-containing sublingual film, was approved in 2015 for the management of severe pain that is resistant to other options. Compared to other BUP-containing sublingual products, Belbuca® has a higher absolute bioavailability, ranging from 46 to 65% [38].

Toxicity

As BUP prescribing has increased, so have emergency department visits involving buprenorphine. Data from the Drug Abuse Warning Network showed that emergency department visits involving BUP increased from 3161 in 2006 to 30,135 in 2010 [39]. This increase coincided with not only an increase in the number of BUP prescriptions but also an increase in illicit use of BUP [40]. Daniulaityte et al. reviewed internet discussions of BUP and found that BUP-related posts peaked in 2011 with 68% of posts discussing the use of BUP to self-treat opioid withdrawal [41]. Despite the rise, the overall rate of illicit BUP use among the IV drug using community is rare, with the majority of users reporting use of BUP to manage withdrawal symptoms as opposed to seeking an euphoric effect [42]. Conversely, BUP use in incarcerated individuals is common, with individuals inhaling or insufflating BUP in order to obtain a long-lasting high [43].

Despite being an opioid, single ingestion BUP-related morbidity and mortality is rare. Per the 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (AAPCC NPDS) 33rd report, there were no reported deaths involving single-substance BUP exposure and only 56 major clinical outcomes, defined as "the patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement" [44]. Paone et al. retrospectively tested consecutive drug overdose cases through the New York City Office of the Chief Medical Examiner from June through October 2013 for BUP and norbuprenorphine and found that only 2% tested positive for BUP metabolites. Importantly, each case involved multiple substances [45]. In adults, BUP has a ceiling effect where higher doses do not cause increased levels of respiratory depression or euphoria [46–48]. This pharmacologic effect is secondary to its *partial* μ-opioid receptor agonism and is a protective mechanism for opioid-induced respiratory depression and failure. This protection, however, does not apply in individuals who concomitantly use sedative agents like benzodiazepines or ethanol [49–51].

Unlike adult patients, unintentional pediatric BUP exposures can lead to significant morbidity and mortality [52–56]. In 2013, Lavonas et al. performed a retrospective root cause analysis of unintentional pediatric BUP exposures utilizing data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System Poison Center Program and Reckitt Benckiser Pharmaceuticals' pharmacovigilance system. They found that buprenorphine/naloxone combination tablets had the highest rates of exposure, when controlled for drug availability, and the most commonly identified root cause was medication that was stored in plain sight. Adverse effects included lethargy (82%), respiratory depression (43%), miosis (37%), and emesis (28%). There were four deaths in their cohort [57].

Among unsupervised oral prescription medication ingestions by children < 6 years of age that required hospitalization, 7.7% were due to BUP, the highest percentage of any single agent examined [58]. Due to the increasing number of pediatric

exposures to the tablet formulation of buprenorphine/naloxone (e.g., Suboxone®), Reckitt Benckiser (the pharmaceutical company responsible for Suboxone®) discontinued the tablet formulation in 2012, directing patients to the film [59]. Fortunately, interventions aimed at reducing unintentional pediatric exposures, like unit-dose packaging, which began in 2013, and the development of medicated film strips, may be working. Budnitz et al. compared emergency department visits for unintentional pediatric BUP exposures before and after these packing and formulation changes and found that visits decreased by 65.3%, after accounting for prescribing frequency [60].

A more recent publication by Toce et al. examined a single-center cohort of pediatric patients with report of unintentional BUP exposure and found higher rates of respiratory depression (83%). In their cohort, median time from reported exposure to respiratory depression was about 4 h, but 25% of patients had onset of respiratory depression more than 8 h after reported exposure. Use of naloxone was common, with 55% of patients receiving at least one dose of naloxone. Despite the fact that a quarter of patients had onset of respiratory depression greater than 8 h from reported exposure, the vast majority (86%) of patients who received naloxone did so within the first 4 h and only two patients received naloxone more than 8 h from time of exposure [61].

The conflicting effects seen in children and adults might be explained by the dramatic difference in the mg/kg administered dose between each group; a 10-kg toddler inadvertently exposed to an 8 mg BUP tab would receive a massively supratherapeutic dose compared to a 70-kg adult. The observed differences in toxicity between children and adults may also be related to the ontogeny of P-glycoprotein (P-gp). P-glycoprotein functions as an effective efflux transport preventing many different xenobiotics, including BUP, from crossing the blood-brain barrier thereby minimizing the severity of respiratory depression. P-glycoprotein concentrations increase throughout gestation; adult postmortem brain cortex tissue has significantly higher P-gp staining than fetal and infant (age 0–3 months) tissue [62–64]. In a murine BUP model, blockade of this efflux transporter leads to increased respiratory depression from BUP [36, 65]. The decreased concentration of P-gp in infants and in the pediatric brain may lead to an increase in cerebral BUP and its major metabolite, norbuprenorphine, resulting in respiratory depression and increased toxicity. In addition to P-gp expression, it is possible that polymorphisms in the *ABCB1* gene that codes for P-gp may account from some of the variable respiratory depressive effects of BUP as individuals with certain mutations in the *ABCB1* gene can have greater respiratory depression after receiving IV fentanyl, a P-gp substrate [66].

Testing/Management

Buprenorphine does not share chemical structure similarity to morphine and therefore a standard urine immunoassay for opiates will be negative in individuals who use BUP. If there is concern regarding adherence to BUP therapy, or an unintentional exposure in the pediatric population, physicians should order a urine or serum specific screen for BUP or norbuprenorphine. Serum and urine BUP levels can be obtained, but results typically take several days, limiting clinical utility.

The majority of adult patients who present with isolated BUP exposure are unlikely to develop significant respiratory depression and most can be monitored in the emergency room setting and safely discharged after a period of observation [67]. When BUP overdose results in respiratory depression, reversal can be accomplished with naloxone [68]. Because of BUP's high affinity for the μ-opioid receptor, larger doses of naloxone (2–4 mg) should be used to reverse respiratory depression [69]. Interestingly, there appears to be a U-shaped dose-response curve for reversal of BUP's respiratory depressant effects. Doses of naloxone over 4 mg demonstrate a reduced ability to antagonize BUP-induced respiratory depression [68]. In the context of mixed ingestions with BUP and other sedative-hypnotics or opioids, physicians should have a low threshold for prolonged observation for potential delayed respiratory depression. In the context of mixed overdoses where BUP is found in combination with other sedative-hypnotics, administration of naloxone will only reverse the sedation associated with BUP. Patients, therefore, may be perceived to have "failed" a naloxone challenge where they may still be experience respiratory depression from a non-opioid agent.

Due to the risk of delayed respiratory toxicity, we recommend that all pediatric patients with possible exposure to BUP be admitted for overnight observation. In the event patient develops depressed mental status or respiratory depression, 0.1 mg/kg IV naloxone should be administered and repeated as necessary to ensure that the patient is protecting their airway and is maintaining adequate ventilation. Adult patients who are maintained on BUP should be counseled on the importance of safe opioid storage because prescription opioid pain relievers are frequently accessible to young children [70].

Methadone

Introduction

Methadone is a long-acting synthetic μ-opioid receptor agonist used in the management of pain and opioid use disorder. Methadone has been found to be efficacious in retaining individuals in treatment programs, decreasing illicit opioid use, and reducing all cause and overdose mortality [71–73]. Methadone has been used as therapy for neonatal abstinence syndrome [74].

The starting dose for methadone used as MAT is 15–30 mg daily, adjusted every 3–5 days as needed to control side effects and withdrawal symptoms. A typical maintenance dose is 80–

100 mg/day [26]. Methadone is traditionally dispensed from methadone clinics, where patients must present each day for their prescribed dose, although individuals who demonstrate medication adherence can qualify for take-home doses. Despite the proven benefits of methadone in treating opioid use disorder, the regulatory burdens of opening a clinic, a lack of community support, a limited number of available spaces, and social stigma continue to limit its use [75].

Pharmacology

Methadone is supplied as a racemic mixture of two enantiomers (R- and S-), with R-methadone possessing 10× the affinity for the μ-opioid receptor [76]. Additionally, methadone antagonizes the *N*-methyl-D-aspartate receptor, in vitro [77]. Unlike BUP, which is a *partial* μ-opioid receptor agonist, methadone is a full opioid agonist. Liquid and pill methadone formulations reach maximal plasma concentration in 2 and 3 h, respectively. [78–80]. Methadone has high oral bioavailability (> 80%) and has a long, albeit variable, half-life (7–65 h) [78, 79, 81]. Methadone is highly protein bound, limiting extracorporeal elimination as a treatment for overdoses [82, 83].

Methadone is primarily metabolized by phase I metabolism utilizing CYP 2B6 producing the inactive metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) [84]. Minor routes of metabolism include CYP 3A4, 2C9, and 2C19 [81]. The *CYP2B6* gene is highly polymorphic, with 60% of some populations expressing a deficient gene (*CYP2B6*6*) [85]. Patients with the *CYP2B6*6* polymorphism are poor metabolizers and can have increased plasma methadone concentrations compared to wild-type individuals [86, 87]. Various drug-drug interactions affect methadone's metabolism. Co-administration of the CYP 2B6 inhibitor sertraline has been shown to increase methadone plasma concentrations [88, 89]. CYP 3A4 inducers (e.g., anti-epileptic drugs: phenobarbital, carbamazepine, oxcarbazepine, phenytoin; anti-virals: nevirapine, efavirenz, ritonavir) accelerate methadone metabolism and have been shown to precipitate withdrawal in methadone-dependent patients [90, 91]. Cytochrome P450 3A4 inhibitors can lead to opioid toxicity. Herrlin et al. reported on a 42-year-old female on chronic methadone therapy (140 mg/day) who developed profound sedation and respiratory depression that was reversed with 0.4 mg IM naloxone after starting ciprofloxacin, a known inhibitor of CYP 3A4, for urosepsis [92, 93].

Toxicity

Toxicity from methadone use results in significant respiratory depression, cardiotoxicity, sensorineural hearing loss and hypoglycemia. Between 2002 and 2006, distribution of methadone increased 25% per year while methadone-associated deaths increased 22% per year. [94]. In 2006, the FDA released new recommendations regarding the prescription of methadone due to the increase in number of deaths involving patients using methadone prescribed for pain. The sales of methadone peaked in 2007 and have declined each year thereafter. Unfortunately, fatalities involving methadone remain common; of the single-substance opioid overdose deaths in patients prescribed an opioid for pain relief, nearly 40% of these deaths involved methadone in 2009, despite only representing 9.8% of morphine milligram equivalents distributed among the referenced states [95].

Respiratory depression in methadone overdose or illicit use is due to excessive agonism of μ-opioid receptors. While BUP has a ceiling effect limiting respiratory depression and euphoria, no such ceiling effect exists for methadone. Non-medical users of methadone will present with typical findings of the opioid toxidrome, including lethargy and respiratory depression [67]. Mortality is not limited to non-medical users; patients initiating opioid substitution therapy are at increased risk of death, particularly during the first 4 weeks of treatment. Risk of death is also increased in the first 4 weeks after discontinuing treatment [73, 96].

QTc prolongation is a known side-effect of methadone [97]. Methadone prolongs the QTc through blockade of currents through the *human ether-a-go-go-related gene* (hERG) potassium rectifier channel (I_{Kr}) [98]. Recently, Isbister et al. used 12-lead Holter recordings to measure the QTc in 19 patients prescribed methadone (median daily dose 110 mg) and compared it to 20 patients prescribed BUP and 19 controls and showed that methadone was associated with prolonged QTc intervals [99]. In their study, QTc prolongation was not associated with methadone dose. Other studies have shown an association between methadone dose and degree of QTc prolongation. Anchersen et al. examined the prevalence of QTc prolongation among patients in opioid maintenance therapy, which consisted of either methadone or BUP. In their methadone cohort, nearly 50% had a QTc > 450 ms with 4.6% having a QTc > 500 ms. No patient receiving BUP had a QTc > 450 ms. Further, they found a positive dose-dependent association between methadone dose and QTc prolongation; all patients with a QTc > 500 ms were given a dose of 120 mg of methadone or greater [100]. Florian et al. analyzed data obtained from five prospective studies, each of which included individual methadone concentrations and multiple Fridericia rate-corrected QT (QTcF) data points, to assess the relationship between methadone dose and QTcF. Based off of their model, they estimate that a methadone dose of > 120 mg/day would increase the QTcF by > 20 ms. Doses of 160–200 mg/day would cause a change of > 60 ms to the QTcF with 0.3–2% of patients having a QTcF of > 500 ms [101]. This increase is not trivial as a QTc > 500 ms has been associated with syncope, cardiac arrest, torsades de pointes (TdP), and sudden cardiac death [102,

103]. Methadone has also been associated with TdP, particularly in patients receiving high (> 100 mg/day) doses [104, 105].

Methadone-associated hypoglycemia is a rare adverse event of methadone exposure. In cancer patients receiving methadone for pain control, methadone was associated with hypoglycemia [106]. Patients are particularly vulnerable during periods of dose escalation [107]. Additionally, hypoglycemia has been reported in cases of unintentional pediatric ingestion. One report detailed the case of an 11-month-old male who became hypoglycemic (serum glucose concentration 17 mg/dL) after unintentional methadone exposure. Interestingly, the patient was hyperinsulinemic, suggesting that methadone my induce insulin secretion [108]. This is in agreement with another report of methadone-associated hypoglycemia with inappropriately elevated insulin levels in a 39-year-old female on chronic methadone therapy for pain [109]. A point of care glucose measurement should be obtained early in cases of severe methadone exposure.

Management

Treatment of methadone overdose involves close monitoring of patient's oxygenation and ventilation. Naloxone should be used in cases of bradypnea/respiratory failure, although care must be taken so as not to precipitate opioid withdrawal in opioid-dependent patients. Given methadone's long half-life, naloxone infusions may be required. Our practice is to take two thirds of the effective reversal dose and infuse it over an hour [110]. Particular attention should be paid in polysubstance ingestions/exposures involving methadone and benzodiazepines as naloxone will only reverse the opioid effects [49]. Due to the risk of QTc prolongation and TdP, electrocardiograms (ECG) should be obtained on patients whose daily methadone dose exceeds 100 mg/day or present with acute methadone overdose [111]. Additionally, all QTc-prolonging medications should be discontinued, and electrolytes, including potassium, magnesium, and calcium should be repleted as necessary. A reasonable goal serum magnesium concentration is 2 mEq/L, although the optimal magnesium concentration for treating TdP is unknown. If a patient progresses to TdP, they should be rapidly assessed and, if hemodynamically stable, administered a single bolus of 2 g IV magnesium sulfate over 2–3 min. This can be repeated. Magnesium infusions for the treatment of TdP have been reported in the literature [112–114]. In the event that the patient develops sustained TdP, becomes symptomatic (e.g., decreased level of consciousness), or pulseless, defibrillation is necessary. It is important to note that there is significant variability in the treatment of drug-induced QTc prolongation and TdP with the majority of treatment recommendations being extracted from non-human studies and case series [115].

Central Alpha$_2$-Adrenergic Agonists

Clonidine

Introduction

Clonidine is marketed and approved by the FDA for the treatment of hypertension and the treatment of attention-deficit hyperactivity disorder (ADHD) in children. Because of it α-adrenergic agonism, clonidine is also an effective agent that is used off-label for management of withdrawal from opioids [26, 116].Clonidine is particularly effective at decreasing signs and symptoms of excessive autonomic activity (e.g., anxiety, tachycardia, chills, piloerection, hypertension) and as a result is used to help manage acute opioid withdrawal. Patients are started on 0.1 to 0.2 mg every 4 h while being monitored for bradycardia and/or hypotension [26]. Adverse effects include sedation, dry mouth, hypotension, and dizziness [116].

Pharmacology

Clonidine is an imidazoline with central α-adrenergic agonism. Clonidine's oral bioavailability is 70–80% with peak plasma concentrations occurring 1 to 3 h from administration [117]. There is moderate protein binding (20–40%). Roughly half of the absorbed dose is metabolized in the liver with the remainder being excreted unchanged in the urine. Elimination half-life ranges from 5 to 20 h [118–121].

Clonidine exerts its cardiovascular effects through its action as an α_2-adrenergic receptor agonist as well as its action on the imidazoline-1 receptor (I-1) [122]. Alpha$_2$ receptors are found throughout the central nervous system (CNS) with high concentrations in the locus ceruleus in the pons as well as the nucleus tractus solitarii in the medulla. Agonism of these receptors in the locus ceruleus by the α_2-adrenergic receptor agonist dexmedetomidine induces sedation in rats [123]. Stimulation of presynaptic α_2-adrenergic receptors in the nucleus tractus solitarii limits the release of norepinephrine, which contributes to the decrease in blood pressure and heart rate [124]. In addition to binding to α_2-adrenergic receptors, clonidine binds to the I-1 receptor and this binding is involved in the anti-hypertensive effects of clonidine [125]. The I-1 receptor is in the rostral ventrolateral medulla within the CNS and in the periphery. Binding of clonidine to the I-1 receptor leads to hypotension, bradycardia, and decreased myocardial contractility [122, 126, 127]. Clonidine may also interact with the endogenous opioid system. In animal models, naloxone can reverse the hypotensive and analgesic effects of clonidine, suggesting that clonidine may induce release of endogenous opioids [128–131]. These results have not been consistently replicated in humans. Clonidine has been shown

to potentiate the effects of morphine and oxycodone. This effect is blocked by yohimbine, a selective α_2-adrenergic receptor antagonist, indicating a role for the α_2-adrenergic receptor in clonidine-mediated analgesia [132, 133].

Toxicity

The toxicity of clonidine is an extension of its therapeutic use. Patients can develop CNS depression, miosis, respiratory depression, bradycardia, and hypotension [118]. Occasionally, initial hypertension has been reported, likely due to peripheral agonism of α-adrenergic receptors [134, 135]. Data on adult clonidine overdoses is limited. A recent report published by Isbister et al. examined clonidine ingestions (both isolated and with co-ingestions) in patients greater than 15 years of age and found that while CNS depression and bradycardia were common (55% and 68%, respectively), serious adverse health outcomes were rare. In their cohort, the median duration of bradycardia was 20 h and the degree of bradycardia was associated with the dose ingested [136].

Severe hypertensive emergency has been reported, but only in the setting of a medication filling error when clonidine intended for an intrathecal pump reservoir was inadvertently injected subcutaneously [137, 138]. The mechanism of clonidine-induced hypertension remains unsolved, although it is postulated that massive doses of clonidine can lead to agonism of peripheral adrenergic receptors and increased vascular tone.

Unintentional pediatric exposures to clonidine are common. There were 3938 ingestions involving clonidine in patients less than 20 years of age in 2015 [44]. In one study, clonidine was the second most commonly implicated medication that resulted in emergency hospitalization for unsupervised prescription medication ingestion in children less than 6 years of age [58]. Wang et al. examined the national trends in pediatric exposures to three common α_2 adrenergic receptor agonists (clonidine, guanfacine, and tizanidine) and found moderate or major effects in nearly 20% of clonidine ingestions, with CNS depression (45.3%), bradycardia (10.2%), and hypotension (8.5%) being the most common signs and symptoms [139]. Despite this, interventions like intubation and the use of vasopressors were rare.

Due to its use as a second-line treatment for ADHD in pediatric patients, clonidine can be compounded to a liquid formulation, introducing the possibility of compounding errors as a source of overdose. Romano and Dinh describe a case of a 1000-fold compounding error that lead to significant toxicity in a 5-year-old male. The compounding pharmacy substituted milligrams for micrograms when preparing the medication, and the patient required multiple boluses of atropine and a naloxone infusion [140].

Management

Treatment of clonidine overdoses involves careful assessment of ventilation and oxygenation, peripheral perfusion, and mental status. The need for vasopressors is rare and most patients are able to maintain adequate blood pressure with IV fluid resuscitation. Endotracheal intubation should be performed if clinically indicated, although this is rare. Bradycardia is common but can be tolerated if peripheral perfusion is adequate. In the event of symptomatic bradycardia, atropine can be used to augment heart rate. Finally, naloxone can be used in cases of severe poisoning to reverse hypotension, bradypnea, and CNS depression, although its efficacy is debatable [134, 136, 141]. Seger and Loden recently published a retrospective analysis of the use of high dose (> 10 mg) IV naloxone in pediatric clonidine exposures. They found that naloxone reversed CNS depression in ~ 80% of patients and documented no adverse effects, even with high doses of naloxone [142]. We recommend IV naloxone with a starting dose of 2–4 mg titrated to a reversal of CNS depression in symptomatic pediatric patients with clonidine exposure. In adult patients, care should be given in administering naloxone especially in the individual maintained on opioids, or those with OUD, as this will precipitate withdrawal. In adult patients, supportive care with IV fluids and, if needed, vasopressor support, may be the most prudent approach.

Lofexidine

Lofexidine is a structural analog of clonidine that functions as a central α_2-adrenergic receptor agonist. Originally marketed as an anti-hypertensive agent, it was approved in 1992 in the UK for the treatment of opioid use disorder [143]. In May 2018, the FDA approved it as the first non-opioid treatment for the management of opioid withdrawal symptoms [144].

Several randomized double-blinded studies compared lofexidine and clonidine in the treatment of opioid withdrawal and found that these drugs had similar effectiveness in controlling signs and symptoms of opioid withdrawal and reducing doses of methadone [145–147]. With regard to adverse effects, hypotension was less common with lofexidine compared to clonidine. Other adverse effects include dizziness and dry mouth [116]. QTc prolongation has been reported when lofexidine is combined with methadone [148].

Given the mechanistic similarities, overdose with lofexidine would be expected to cause similar signs and symptoms to clonidine, although detailed reports of lofexidine overdose are lacking. Treatment should focus on good supportive care with careful assessment of the patient's airway, breathing, and circulation. Although there is no evidence to support its use, IV naloxone could be considered in cases of severe

toxicity, with the understanding that it may produce opioid withdrawal in those individuals with opioid dependency.

Alternative Agents

Loperamide

Introduction

Loperamide was first synthesized in 1969 and has been available without a prescription since 1982. Loperamide is FDA approved for the treatment of diarrhea and is used off-label in the treatment of opioid withdrawal. Anti-diarrheal doses range from 4 to 16 mg/day, which is far lower than the 200–400 mg/day reported with loperamide abuse [26, 149].

Pharmacology

Loperamide is a phenylpiperidine derivative that is used in the treatment of diarrhea [150, 151]. Structurally, it resembles a combination of haloperidol (a neuroleptic) and isopropamide (an anti-cholinergic). Loperamide's oral bioavailability is low (< 1%) due to considerable first-pass metabolism. Systemic absorption is further limited by P-gp, which decreases gastrointestinal uptake and enhances elimination through bile excretion. Loperamide is highly lipophilic, is extensively protein bound (97%), and is metabolized in the liver via CYP2C8 and CYP3A4 to desmethylloperamide [152, 153].

Loperamide exerts its anti-diarrheal effects by decreasing motility and fluid secretion via binding to μ-opioid receptors in the myenteric plexus as well as modulation of enteric 5-hydroxy-tryptamine release [154, 155]. In addition to the gastrointestinal tract, loperamide binds to peripheral μ-opioid receptors, providing analgesia [156, 157]. Loperamide is *able* to bind to brain μ-opioid receptors, but brain concentrations are kept low via the activity of P-gp [155, 158, 159]. As such, traditional opioid effects like CNS depression and bradypnea are rare with therapeutic dosing. Administration of the P-gp inhibitor quinidine increases intestinal absorption and enhances CNS entry at the blood-brain barrier leading to respiratory depression [160].

In addition to binding to μ-opioid receptors, loperamide binds to and inhibits the hERG-encoded subunit of the I_{Kr} as well as the voltage-gated fast sodium channel, in vitro [161–163]. Inhibition of the fast sodium channel leads to impaired ventricular depolarization and widening of the QRS while blockade of the I_{Kr} leads to ventricular repolarization delay and QTc prolongation. QRS widening and QTc prolongation have been reported in loperamide overdoses [164–167]. Loperamide's effect on the cardiac conduction system is responsible for much of the morbidity and mortality associated with loperamide overdoses.

Toxicity

The use of loperamide for recreational purposes (e.g., to get "high") and to combat opioid withdrawal is increasing. Using a web-based study, Daniulaityte et al. reported on the dramatic increase in web-based discussions and posts related to the non-medical use of loperamide. They found that users primarily discussed the use of loperamide to treat opioid withdrawal, but that some users were discussing the potential to "get high" [168]. A retrospective review of intentional loperamide ingestions reported to the California Poison Control Systems between 2002 and 2015 showed a sharp increase in the number of calls in 2014. Over the entire study period, three deaths were reported as well as nine reports of patients who developed cardiotoxicity. The ingestion size ranged from 200 to 400 mg/day [149].

This recent increase in use has been substantiated on a national level as well. Vakkalanka et al. queried the AAPCC NPDS for reports of intentional misuse, abuse, and suspected suicide between January 1, 2010 and December 31, 2015 involving loperamide and found a 91% increase in reported exposures. Single-agent loperamide exposures increased at a rate of 25 cases per year while polysubstance ingestions involving loperamide increased at a rate of 13 cases per year. There were 15 deaths in the study period, with 8 involving single-agent loperamide exposure [169].

Ventricular dysrythmias are an increasingly recognized complication of loperamide overdose through prolongation of the QRS and QTc intervals. Prolongation of the QRS can lead to ventricular tachydysrhythmias and QTc prolongation can induce TdP. Marraffa et al. presented a case series of five patients with loperamide abuse, three developed life-threatening cardiac arrhythmias (monomorphic and polymorphic ventricular tachycardia). Loperamide concentrations ranged from 22 to 130 ng/mL (levels obtained in four of the five patients) [165]. For reference, a therapeutic dose of four 2 mg tabs of loperamide leads to a peak plasma concentration of 1.18 ± 0.37 ng/mL [170]. Wightman et al. reported the case of a 48-year-old woman who presented with somnolence and weakness and reported ingesting 20–40 2 mg tabs of loperamide a day for several weeks. Her initial ECG was notable for a QRS 164 ms and a QT 582 ms. She had several runs of non-sustained ventricular tachycardia that did not require intervention. Her serum loperamide concentration was 210 ng/mL [167]. Finally, Bhatti et al. described the use of isoproterenol to prevent bradycardia-induced arrhythmias in a 37-year-old woman who presented after ingesting ~ 200 tabs of 2 mg loperamide. Her ECG was notable for a QTc > 600 ms. Labs were notable for a negative loperamide concentration, but a desmethyllopermide level of 32 ng/mL [164].

Loperamide overdose may be lethal. Eggleston et al. reported on two deaths involving supratherapeutic loperamide ingestion in individuals self-treating OUD. The first was a 24-

year-old male found pulseless and apneic who had been using loperamide as an opioid substitute. Postmortem cardiac blood analysis revealed a loperamide concentration of 77 ng/mL, in addition to clonazepam and buprenorphine. The second patient was a 39-year-old male who "suddenly gasped" and collapsed at home. CPR and resuscitative efforts were unsuccessful. Postmortem toxicology was positive for a loperamide level of 140 ng/mL [171]. Bishop-Freeman et al. published on 21 loperamide-related deaths in North Carolina and found the median loperamide peripheral blood concentration to be 0.23 mg/L (230 ng/mL). They also report on the use of various P-gp inhibitors (e.g., quinine/quinidine) that are used to enhance the loperamide high by blocking P-gp-mediated efflux of loperamide from the CNS [172].

Management

Treatment of loperamide toxicity is largely supportive and should include careful assessment of patient's airway, breathing, and circulation. Naloxone should be used when bradypnea or respiratory depression/failure are present [164, 173]. The lowest effective dose should be used in opioid-dependent individuals to avoid precipitating withdrawal. Management of loperamide-associated cardiotoxicity is anecdotal and based on therapies for other drugs that prolong the QRS and QTc. There is no specific antidote for loperamide. An ECG should be obtained early in the clinical course. In cases of QTc prolongation, the recommendations included in the methadone section should be followed. Temporary transcutaneous cardiac pacing as well as isoproterenol can also be used to augment the heart rate and has been shown to provide some benefit in the setting of loperamide-induced dysrhythmias [149, 174, 175]. If the patient's QRS is prolonged, a trial of sodium bicarbonate (50–100 mEq) is a reasonable, with either repeated boluses or a bolus and continuous sodium bicarbonate infusion of 150 mEq of sodium bicarbonate in 1 L of 5% dextrose (D5W) to infuse at 150 cm^3/h if there is clear shortening of the QRS. It is unknown whether sodium bicarbonate is beneficial in treating loperamide-induced QRS widening as patients typically receive a multitude of therapies [176, 177]. Hemodialysis is unlikely to be effective at removing drug given loperamide's high degree of protein binding and large volume of distribution.

Kratom

Introduction

Kratom (*Mitragyna speciosa* Korth) is a plant native to Southeast Asia that has long been consumed for its stimulant and analgesic properties [178]. It is used informally in the USA to reduce or abstain from non-prescription opioid or heroin use, manage chronic pain, or mitigate opioid withdrawal [179–181]. Outside of the USA, kratom has gained popularity in Southeast Asia as a method to manage withdrawal from opioids as well as a means to induce euphoria [182]. Kratom can be purchased through internet pharmacies in addition to local head shops [180, 183]. It comes in the form of leaves that can be chewed, smoked, brewed into tea, or mixed with coffee or sweetened beverages [182].

Pharmacology

Kratom contains multiple indole alkaloids, with the principle psychoactive components being mitragynine and 7-hydroxymitragynine [184]. The antinociceptive properties of mitragynine and 7-hydroxymitragynine arise from agonism at the μ-, δ-, and κ-opioid receptors. Additionally, mitragynine binds directly to α_2-adrenergic receptors (agonism) and serotonin receptors (antagonism) in the bulbospinal descending pathway [179, 185–188]. Mitragynine has one fourth the potency of morphine, while 7-hydroxymitragynine has ~ 10× the potency of morphine [189, 190]. Mitragynine is rapidly absorbed with a time to maximum plasma concentration of approximately 0.8 h. It is extensively distributed throughout the body (volume of distribution ~ 38 L/kg). Both phase I and phase II metabolism take place and multiple different metabolites have been identified [184, 191].

Toxicity

Kratom exposures reported to the AAPCC NPDS are increasing. Anwar et al. examined AAPCC NPDS and found that calls reported to US poison control centers involving kratom increased 10-fold between 2010 and 2015 [192]. Users of kratom range from individuals looking to get high, treat chronic pain, treat opioid dependence, or mitigate opioid withdrawal symptoms [179, 180]. In 2007, Vicknasingam et al. performed a cross-sectional survey of active kratom users in Malaysia. They found that 90% of short- and long-term users reported using kratom to reduce addiction to other drugs while 84% reported using kratom to alleviate opioid withdrawal symptoms [193]. Unfortunately, kratom use itself can lead to dependency, development of withdrawal symptoms, and craving [194].

The physical effects of kratom vary depending on the dose ingested. In low doses (1–5 g of plant product), stimulant effects predominate, with users experiencing increased alertness, productivity, sociability, and sexual desire. In higher doses (5–15 g of plant product), opioid effects prevail [184]. Serious morbidity and mortality has been reported, but cases are often confounded by co-ingestions. Seizures have been reported [179, 195], as has intrahepatic cholestasis [196, 197], but to date no mechanism has been identified. Karinen et al. reported on the death of a middle-aged man with history of substance abuse that was found dead in his bed the morning

after consuming kratom. Autopsy identified congested and edematous lungs, with areas of bronchopneumonia. Toxicologic testing confirmed the presence of mitragynine and 7-hydroxymitragynine; zopiclone, citalopram, and lamotrigine were also detected, but these were all within therapeutic ranges [198]. Similarly, McIntyre described the death of a 24-year-old male who died after consuming kratom in addition to venlafaxine, diphenhydramine, and mirtazapine [199].

As an herbal supplement, kratom remains unregulated by the FDA, leading to potential adulterants within products marketed as pure kratom. Lydecker et al. examined several commercially available kratom products and assessed for the amount of mitragynine and the more potent 7-hydroxymytragynine. Several products contained 7-hydroxymitragynine concentrations that far exceeded levels found in naturally occurring plants, suggesting commercial adulteration to generate a more potent product [200]. Similarly, Kronstrand et al. described a case series of nine deaths attributed to a product called "Krypton," which was found to be a combination of kratom and *O*-desmethyltramadol [201].

Management

Treatment of kratom intoxication is largely supportive. Careful assessment of respiratory status should be performed. Benzodiazepines should be administered in the event of seizure activity [195]. Naloxone should be considered if bradypnea is present, although bradypnea has yet to be reported in isolated kratom exposures and the data for the use of naloxone in kratom intoxication is lacking. Isolated kratom ingestions are unlikely to cause significant morbidity, but care must be taken in cases of polypharmaceutical ingestion. As the literature above indicates, the combination of kratom with other sedating xenobiotics can lead to life-threatening CNS depression and respiratory failure.

Gabapentin

Gabapentin has been used with varying levels of success to augment MAT. Gabapentin is a γ-amino butyric acid (GABA) analog although it does not bind to the GABA receptors. Although its exact mechanism of action is not fully elucidated, there is evidence that gabapentin inhibits voltage-gated calcium channels leading to reduced excitatory neurotransmitter release [202, 203]. Kheirabadi et al. performed a double-blind, randomized, placebo-controlled trial of methadone plus 900 mg/day of gabapentin compared to methadone plus a placebo in controlling withdrawal symptoms and found no difference between the treatment groups [204]. In the second phase of the same study, Salehi et al. showed that a higher dose of gabapentin (1600 mg/day) plus methadone was superior in controlling certain symptoms of withdrawal, namely coldness, diarrhea, dysphoria, yawning, and muscle tension compared to 900 mg/day of gabapentin plus methadone [205].

Overuse of gabapentin alone is common with concomitant opioid use. The top predictor of sustained overuse in gabapentin and opioid treated patients was detoxification [206]. In one study of current non-medical users of diverted prescription opioids, 15% reported using gabapentin "to get high" within the past 6 months [207]. Baird et al. studied gabapentinoid (defined as gabapentin or pregabalin) use among patients in six substance misuse clinics in Scotland and found that over 20% of study participants admitted to abusing gabapentinoids and of those patients, nearly 40% used gabapentinoids to augment the high they get from methadone [208]. The combination of opioids and gabapentin has been shown to increase the risk of emergency department visits, inpatient hospitalizations, and/or respiratory depression significantly [209]. Finally, Gomes et al. found that co-prescription of opioids and gabapentin was associated with a 49% increased odds of opioid-related death, with moderate (900–1799 mg/day) dose and high (≥ 1800 mg/day) dose gabapentin exposure being associated with a nearly 60% increase in opioid-related death compared to no gabapentin use [210].

Akuamma

Various alternative plants have been described to alleviate opioid withdrawal. Seeds from the akuamma (*Picralima nitida*) tree extract contain a variety of alkaloids (e.g., akuammidine, akuammine, akuammicine, akuammigine, and pseudoakuammigine) that have mild opioid receptor (μ-, δ-, and κ-) affinity with pseudoakuammigine having analgesic and anti-inflammatory properties [211, 212]. Users describe mild effects similar to those of kratom, with nausea, vomiting, and unpleasant taste being frequently reported [213]. Detailed studies on human toxicity are lacking, but an animal study showed inflammation and necrosis of the liver [214].

Kava

Kava (*Piper methysticum*) is another herbal product that is consumed for its anxiolytic properties and may be used to mitigate opioid withdrawal symptoms [215, 216]. Kava contains several liphophilic kavalactones concentrated in the root of the plant that increase GABAergic tone, inhibit monoamine oxidase B, and block the reuptake of noradrenaline and dopamine. There does not appear to be any direct opioid receptor agonism [217]. Kava is effective at treating generalized anxiety disorder compared to placebo, but its use is limited due to reports of hepatoxicity [218]. Hepatotoxicity was initially thought to be due to extraction techniques that utilized acetone and ethanol, but subsequent case reports have demonstrated

hepatotoxicity with traditional aqueous kava extracts [219–221].

Conclusion

Access to medical management of OUD continues to be limited in the USA. In the face of a persistent opioid public health emergency in the USA, individuals may turn to non-FDA-approved measures to self-manage OUD and withdrawal. Although methadone, buprenorphine, and to some extent clonidine are currently used in the formal management of OUD, innovative individuals have turned to non-medically approved alternatives like loperamide and kratom to manage symptoms of opioid use and withdrawal. Additionally, herbal supplements and pharmaceuticals that produce sedation through GABA stimulation may be increasingly used to manage opioid withdrawal. Inadvertent poisoning from these agents may not present with typical opioid toxidrome features. Instead, a careful investigation of potential herbal supplements and alternative agents in the poisoned individual informally managing OUD or withdrawal should consider potential hepatotoxic or cardiotoxic effects. It is important that emergency providers are familiar with the toxicity of these agents in order to provide timely and accurate care.

Compliance with Ethical Standards

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