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The unsuspected threat of three opioid-like substitutes

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ABSTRACT

The opioid epidemic has left its toll on the United States with millions suffering from an opioid use disorder and tens of thousands dying from overdoses each year. With intentions to combat the crisis, health providers have been prescribing less opioids, which resulted in an unintentional increase in the abuse of other opioid-like substances. Three emerging drugs of abuse have been noted in the literature as having increased abuse potential in light of recent trends. Kratom, an herbal supplement, gabapentin, a prescription nerve pain and anticonvulsant medication, and loperamide, an over-the-counter antidiarrheal medication. These have all displayed opioid-like properties at high doses and used to alleviate opioid withdrawal. Healthcare clinicians and patients might not be aware of the potential risks involved with misusing or abusing these opioid substitutes. This article discusses the increased usage of kratom, gabapentin, and loperamide, the abuse potential, adverse effects and withdrawal symptoms of each drug, and nursing implications that impact inpatient safety and management.

Introduction

In 2016, an estimated 2.1 million people had an opioid use disorder, including 1.8 million people with a prescription pain reliever use disorder (Bose et al., 2016). The same year saw a staggering death toll of 42,249 people killed by opioid overdose, prompting the U.S. Department of Health and Human Services to declare a public health emergency (Jones, Einstein, & Compton, 2018). The so-called opioid epidemic has been called one of the greatest health crises facing the United States, and despite the best efforts of lawmakers, health professionals and regulatory bodies, the complexity of the problem renders any simple solution inadequate.

It's well known that overprescription of pain medication has contributed to the opioid crisis (Makary, Overton, & Wang, 2017). However, past attempts to counter the effects of the opioid crisis have led to unintended consequences. For example, when the United States government cracked down on prescription opioids in 2010 to try and mitigate this phenomenon, the rates of heroin and fentanyl abuse as substitutes rose dramatically, according to the Centers for Disease Control and Prevention (CDC) (Guy et al., 2017).

Recently public consciousness regarding the dangers of opioid abuse has grown, and regulations on opioid prescription have steadily tightened. Inevitably, this has resulted in rising use of opioid substitutes. Opioid-like herbal supplements such as kratom and over-the counter (OTC) medications such as loperamide are increasingly sought to manage chronic pain or opioid withdrawal symptoms (Borron et al., 2017; Smith & Lawson, 2017). Furthermore, in an effort to combat the opioid crisis, health providers have attempted to prescribe more medications with low abuse potential such as gabapentin, though recent literature is showing an increase in gabapentin abuse (Evoy, Morrison, & Saklad, 2017). While these substitutes have high potential for abuse and harm, they carry the public perception of being “natural” and therefore safer than prescription opioids (Fingleton, Watson, Duncan, & Matheson, 2016).

Health care clinicians may not be familiar with the safety and abuse potential of these substances. These opioid alternatives are significantly easier to access compared to going to an authorized detox clinic to receive medication-assisted treatment (MAT). Some of these drugs are not only more affordable, but also have mood enhancing effects. While opioid withdrawal is not life-threatening, it can be extremely uncomfortable and opioid abusers can become desperate to find substances to mitigate withdrawal. The concern is that users who try to self-treat opioid withdrawal may not be aware of the risks, and may develop dependency to these substances. The goal of this article is to inform nurses about the increase in opioid-like substance use, heighten awareness about the adverse effects of various opioid substitutes, and discuss nursing implications that impact patient safety and management in the inpatient setting. Three substances have been selected for review in this article: kratom, gabapentin, and loperamide.

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Kratom

Background

Kratom (*Mitragyna speciosa*) is a tree native to southeast Asia. Its leaves, known for their analgesic properties and euphoric effects, are traditionally used for medicinal and recreational purposes (Smith & Lawson, 2017; Swogger & Walsh, 2018). For centuries, leaves from the kratom tree were chewed raw or ground up and used to make an herbal tea consumed by native laborers to help them work longer days in the sun (Chang-Chien, Odonkor, & Amorapanth, 2017; Swogger & Walsh, 2018). Recent studies show that the leaves of the kratom plant contain the alkaloids mitragynine and 7-hydroxymitragynine, which interact with opioid receptors (Grundmann, 2017).

Though kratom can be taken in a variety of ways, the most common preparation is mixed as a beverage or taken orally in green tea-like powdered form (Grundmann, 2017; Swogger & Walsh, 2018). Currently there are almost no restrictions on the purchase of kratom in the United States. Kratom of varying quality can be found easily in head shops, smoke shops, and can also be purchased online (Singh, Müller, & Vicknasingam, 2014; Swogger et al., 2015). According to the U.S. Drug Enforcement Administration (DEA), kratom is not controlled under the Federal Controlled Substances Act, but is currently labeled a Drug and Chemical of Concern due to its potential for psychosis and death (DEA, 2017; Swogger & Walsh, 2018). The US Food and Drug Administration has not approved kratom for any medical use (DEA, 2017).

Abuse potential and withdrawal

The motivations for kratom use vary, but it is generally used to decrease pain and fatigue, improve mood and alleviate opioid withdrawal symptoms (Grundmann, 2017). Its function as an opioid substitute is well documented. Out of 500 respondents, 68.9% of users used kratom to stop or reduce opioid use, 64.1% used kratom to as an alternative to opioid use, and 18.4% used kratom to reduce chronic pain (Smith & Lawson, 2017).

Adverse effects with kratom use appear to mimic that of opioids with symptoms such as constipation, nausea, and dizziness or drowsiness (Grundmann, 2017; Swogger et al., 2015). Withdrawal effects from kratom begin 12–48 h after cessation of regular use and can last one to three days (Grundmann, 2017; Singh et al., 2014). Symptoms include both physiological and psychological components: sleeping difficulty, nausea, vomiting, sweating, fever, diarrhea, hot flashes, watery eyes, shakiness or tremors, body aches, and nervousness, sadness, restlessness, anger, tension, and depressed mood (Singh et al., 2014).

Gabapentin

Background

With increased reports of overdoses and deaths from opioids, providers have been prescribing gabapentin (Neurontin, Gralise, Horizant) as a safer alternative for managing pain (Goodman & Brett, 2017). While initially indicated for post-herpetic neuralgia and epilepsy, 80–93% of prescriptions for gabapentin have been used off-label for a variety of conditions, including anxiety and substance abuse disorders (Evoy et al., 2017; Vickers Smith et al., 2018). According to the DEA, gabapentin is currently not a controlled substance, indicating low abuse potential. However, recent findings show that gabapentin abuse is increasing due to the medication's ability to produce euphoria and dissociative properties at high doses (Evoy et al., 2017). In response to the growing concerns about gabapentin abuse and misuse, Kentucky and Tennessee have re-classified the drug as a Schedule V controlled substance in 2017 and 2018, respectively (902 KAR 55:015; Tenn. Code Ann. § 39-17-414).

While health providers have been restricting opioid prescription amounts and seeking alternatives with less abuse potential, they may not realize the relative ease patients have in acquiring high quantities of gabapentin that can result in abuse (Evoy et al., 2017). Because gabapentin is so widely prescribed for off label use, the recommended dosages can vary greatly, and it can be prescribed at greater quantities than would be typical for its indicated use (Vallerand & Sanoski, 2018).

Abuse potential and withdrawal

Gabapentin is more likely to be abused by patients with a history of substance abuse, particularly opioid abuse (Evoy et al., 2017). Among United States opioid-dependent patients, gabapentin was misused at similar rates with clonidine and more than double the rate for amphetamine (Wilens, Zulauf, Ryland, Carrellas, & Catalina-Wellington, 2015). Recommended gabapentin doses range from 900 to 3600 mg per day, but in abuse cases, doses as high as 7200 mg per day have been reported (Mersfelder & Nichols, 2016; Vallerand & Sanoski, 2018). With monthly prescriptions, patients can easily abuse gabapentin by taking two days worth of doses at a time.

The motivations for gabapentin misuse and abuse include the medication's capacity to potentiate opioid “highs” and manage drug and alcohol withdrawal symptoms (Wilens et al., 2015). Though gabapentin was initially marketed as safe with limited abuse potential, recent case reports show signs of dependency. A recent review discovered that gabapentin withdrawal symptoms typically begin between 12 h and 7 days after cessation, though the majority occurred between 24 and 48 h (Mersfelder & Nichols, 2016). Frequently reported withdrawal symptoms included agitation, confusion and disorientation, diaphoresis, gastrointestinal symptoms, tremor, tachycardia, and hypertension (Mersfelder & Nichols, 2016). Reinstitution of gabapentin appeared to be the most effective intervention for alleviating withdrawal symptoms (Mersfelder & Nichols, 2016).

Loperamide

Background

Over-the-counter (OTC) medications can be found in grocery stores, gas stations and retail pharmacies. Their convenience and availability make them useful for managing minor ailments, but one drawback to OTC medications is that their easy accessibility belies their potency. Many OTC medications have high potential for misuse and abuse.

Loperamide (Imodium) is an OTC antidiarrheal medication initially deemed to have relatively few adverse effects and low abuse potential despite being classified as a synthetic opioid (Ericsson & Johnson, 1990). It is available in the form of oral tablets, capsules and liquid solutions. It is generally not considered to have abuse potential because at approved doses in adults (up to 16 mg in 24 h), it is metabolized quickly and does not cause central nervous system effects (Borron et al., 2017; Vakkalanka, Charlton, & Holstege, 2017). However, at supratherapeutic doses and when in combination with other drugs, loperamide appears to bypass the blood-brain barrier and cause euphoria (Hughes, Hendrickson, Chen, & Valento, 2018).

Loperamide is also known as the “poor man's methadone” due to its low cost and ability to prevent opioid withdrawal (Borron et al., 2017). Qualitative data collected from a web-based study suggests that loperamide is seen as somewhat of a desperate measure taken by those affected by opioid withdrawal (Daniulaityte et al., 2013).

Abuse potential and withdrawal

Misuse and abuse of loperamide has increased dramatically within the past decade (Vakkalanka et al., 2017) due to its availability OTC and ever-stringent regulations on legitimate opioids. The increase in rates of abuse is partially fueled by the proliferation of information regarding its use as an opioid substitute via online channels. Recent

trends in online forums and calls to poison control centers have shown individuals using 40–100 times the recommended doses to self-treat opioid withdrawal (Borron et al., 2017; Daniulaityte et al., 2013; Idris, Mihora, & Kaye, 2018).

While no major adverse effects are observed at therapeutic levels of the drug, supratherapeutic levels up to 100 times the recommended dose are associated with cardiotoxic events (Idris et al., 2018). The number of calls to poison control centers related to loperamide misuse or abuse alone nearly doubled between 2009 and 2015 (Borron et al., 2017). In response, the U.S. Food and Drug Administration released a safety announcement on June 7, 2016 warning healthcare professionals that individuals abusing or misusing high doses of loperamide in attempts to self-treat opioid withdrawal or achieve a feeling of euphoria are at increased risk for abnormal heart rhythms and serious cardiac events that can lead to death (Food and Drug Administration, 2016).

While common adverse effects with loperamide include nausea, constipation, drowsiness, and headache (Miller, Panahi, Tapia, Tran, & Bowman, 2017; Vallerand & Sanoski, 2018), overdose of loperamide mirrors opioid toxicity with symptoms such as pinpoint pupils, central nervous system depression, and respiratory depression (Eggleston, Clark, & Marraffa, 2017; Miller et al., 2017). Loperamide has also shown potential for dependence in a recent case report describing a man showing narcotic withdrawal symptoms after abrupt cessation and requiring methadone to mitigate withdrawal (MacDonald, Heiner, Villarreal, & Strote, 2015).

Nursing implications

In the inpatient setting, nurses may admit patients who are actively experiencing withdrawal from unknown substances or encounter patients experiencing withdrawal symptoms days after the initial admission assessment. In these instances it is important that nurses know how to care for these patients. Clinical guidelines for assessment, intervention and education regarding inpatient medication safety are discussed further in Table 1.

Intake assessment

Assessment during admission may be complicated by the fact that current toxicology screens have difficulty detecting substances such as synthetic drugs, and herbal and opioid-like drugs (Rosenbaum, Carreiro, & Babu, 2012; Smith & Lawson, 2017). Unanticipated withdrawal symptoms based on toxicology testing may be avoided if nurses ask patients during the initial admission assessment if any supplements besides the prescribed medications are being used. Furthermore, if patients have a known history of substance abuse, nurses should ask patients if they've attempted to alleviate withdrawal symptoms with substances not typically received for detoxification treatment.

With the increased use of alternative opioid-like substances, nurses need to be familiar with common opioid withdrawal symptoms because the presence of symptoms despite negative toxicology screens for opiates may indicate potential opioid-substitute abuse. Withdrawal from opiates and opiate substitutes can be compared to severe influenza due to similarly experienced symptoms. The clinical opiate withdrawal scale (COWS) is an 11-item scale used to rate common signs and symptoms of opioid withdrawal (Wesson & Ling, 2003). The signs and symptoms assessed include resting pulse rate, gastrointestinal upset, sweating, hand tremor, restlessness, yawning, pupil size, anxiety/irritability, joint aches, gooseflesh skin, and runny nose. The summed score can help health professionals determine the severity of opiate withdrawal and assess the level of physical dependence. Withdrawal symptoms typically peak in 24–48 h depending on the half-life of the opioid substance (Sigmon et al., 2012). The symptoms generally diminish in a few days, but symptoms can last for over a week (Kosten & O'Connor, 2003).

Table 1
Clinical practice regarding opioid substitute abuse in the inpatient setting.

Assessment
- Ask about history of substance use[a]
- Check toxicology screens for opioid use
- Check patient belongings for medications/dietary supplements and ask the patient what they are used for
- Ask about any substances (medications or herbals) that have helped manage withdrawal before
- Assess for common opioid withdrawal symptoms[b,c]
  - ➢ Nausea, vomiting, sweating, fever, diarrhea, watery eyes, shakiness or tremors, body aches, fatigue, anxiety, and restlessness
  - ➢ Utilize COWS if opioid withdrawal is suspected[b]

Interventions
Pharmacologic[c,d]
- Clonidine can decrease autonomic overactivity (tachycardia, “gooseflesh”, anxiety, irritability)
- Benzodiazepines and antihistamines can be used for anxiety and insomnia
- Nonsteroidal anti-inflammatory drugs such as ibuprofen can help with pain and discomfort

Nonpharmacologic
- Provide an empathetic and reassuring approach to ease stress and anxiety[c]
- Dim lighting in patient room to help with light sensitivity due to miosis
- Play calming music or use sound machines to reduce agitation and stress[e]
- Offer broth/electrolyte drinks for decreased appetite related to nausea and vomiting

Clinical judgment and education
Inpatient medication safety
When providing PRNs to alleviate pain or anxiety, be aware of medications that can increase CNS depression and respiratory depression
- ➢ For example, a patient with scheduled gabapentin might request to take their PRN oxycodone for chronic pain at the same time- this can increase risk of death[f]
- ➢ Common medications and herbals that can increase CNS/respiratory depression: antihistamines, opioids, sedative/hypnotics, Kava-kava, valerian, chamomile[g]

Education
- Discuss with provider about concerns regarding medication safety for patients during discharge planning
- Educate patient about medications and adverse effects related to drug interactions

[a] Evoy et al. (2017).
[b] Wesson and Ling (2003).
[c] Galanter, Kleber, and Brady (2014).
[d] Schuckit (2016).
[e] Chariyawong et al. (2016).
[f] Gomes et al. (2017).
[g] Vallerand and Sanoski (2018).

Interventions

The most effective approach for treating withdrawal involves using long-acting opioid medications such as methadone and buprenorphine; however, only licensed addiction treatment facilities and health providers who have completed specific training regarding opioid drugs can administer these medications (Schuckit, 2016). In an inpatient setting, nurses should discuss with health providers about medication to provide comfort such as clonidine (Catapres) or tizanidine (Zanaflex) for autonomic overactivity (“gooseflesh”), benzodiazepines or other sedating drugs for anxiety and insomnia, and loperamide (Imodium) for diarrhea (Schuckit, 2016). For nonpharmacological comfort, nurses can dim lighting and administer eye drops to provide comfort to sensitive eyes. Music can also be therapeutic for calming anxiety and agitation (Chariyawong, Copeland, & Mulkey, 2016).

Clinical judgment and education

Nurses should also be aware that common OTC drugs such as loperamide are being combined with other over the counter drugs and supplements to increase serum concentrations and potentiate the euphoric effects (Hughes et al., 2018). Nurses should monitor for patients

requesting both gabapentin and other central nervous system depressants such as opioids for pain or benzodiazepines and antihistamines for anxiety (Vallerand & Sanoski, 2018). Gabapentin is often prescribed as an adjunct with opioids for chronic pain management, but combined use has been found to increase risk of death from accidental opioid overdose by 49% (Gomes et al., 2017). Nurses and providers may not be aware that gabapentin and opioids can both cause respiratory depression. Clinicians should educate patients about the potential risks of gabapentin abuse, dependency, and interactions with other medications. Nurses should also advocate for patients with their providers by discussing potentially unsafe medication interactions, such as herbal supplements or other drugs in adjunct therapy with opioids.

Conclusion

Research regarding the abuse and clinical effects of kratom, gabapentin, and loperamide is limited, particularly in nursing. Further research of trending drugs of abuse is necessary to better understand the unexpected effects of the opioid crisis and management of opioid-like substitutes.

As regulations on opioids tighten, ever-desperate sufferers of opioid addiction will continue to seek substitutes to fill the need or to reduce withdrawal symptoms. Clinicians have a responsibility to stay informed about these trends and developments in the face of an ongoing opioid crisis. Understanding the use and significance of these opioid substitutes can mean the difference between life and death for our patients. Armed with this knowledge, nurses will be able to help both providers and patients make informed, potentially life-saving decisions regarding the use of opioid substitutes.

Declaration of interest

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