5-2020

The Opioid Epidemic: Long Term Implications

Sana Abbas
Philadelphia College of Osteopathic Medicine

Philadelphia College of Osteopathic Medicine
Graduate Program in Biomedical Sciences
School of Health Sciences

The Opioid Epidemic: Long Term Implications

A Capstone in Neurobehavior Concentration by Sana Abbas

Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Sciences, Neurobehavior Concentration
May, 2020

ABSTRACT

The use of opioid medications is a rapidly growing problem in the United States. Although these medications are effective for short term pain relief, their long-term implications on the brain and interactions with other substances are still unknown. Despite the gaps in knowledge of the long-term implications or efficacy of opioids, there are still more than 200 million prescriptions written annually for opioid analgesics (Semenkovich et al., 2014). In addition to the overuse of these medications, they can cause interactions with other substances, some of which can cause severe cases of poly-intoxication. As the use of these medications continues to increase, so does the number of deaths that result from the misuse of these medications. According to the American Medical Association, "after alcohol intoxication, opioids are the most common cause of poisoning in presenting to North American emergency departments" (Lewis et al., 2015). This increase in emergency department usage as a result of opioid-related cases leads to an overall increase in healthcare costs. While researching the long-term effects of opioids on the brain, their interactions with other substances, and potential side effects that can arise from prolonged opioid usage, more concrete options must be considered. Finding effective ways to treat these patients and using alternative methods for pain relief can not only help people in need of pain relief but also our healthcare system as a whole.

INTRODUCTION

The use of opioid analgesics is a rapidly growing problem in the United States. Although these medications are effective for short term pain relief, their long-term implications on the brain and interactions with other substances are still unknown. While it is understandable that

pain relief is an essential part of healthcare, it can also be a complicated topic to address due to its subjectivity. As the amount of analgesics available to the population continues to grow, so do the number of options available for pain relief. Although we know a substantial amount of information about how these medications work, we can never completely understand how an individual will react to pain medications, especially when it comes to opioid analgesics due to the differences in each person's brain chemistry. With the growing use of prescription opioid medications, the potential for abuse also increases. While there is little information on the cost of nonmedical use of prescription opioids, the few studies that have been done on this subject have shown extremely high costs associated with this. Research shows that the economic cost of the nonmedical use of prescription opioids in the United States alone is more than $50 billion annually (Hansen et al., 2011).

To understand the opioid epidemic, we must first understand how opioid mediations impact the brain. While every patient will respond to an opiate differently, a basic understanding of the neurological implications of opioid usage is crucial in deciphering how these medications work. When opiates of any kind are used, they are broken down into chemicals that travel through the bloodstream to the brain, where they attach to opioid receptors. The mu-opioid receptor is the main target for morphine, heroin, and most other opioid analgesics. While all individuals have these receptors in their brains, differences in genetic makeup can cause variations in the mu-receptor. This binding of the chemicals with the target receptors triggers the mesolimbic reward system, the biochemical pathway associated with reward and pleasure. Once activated, this pathway generates signals in the ventral tegmental area (VTA), which results in the release of the neurotransmitter dopamine from the nucleus accumbens; this release of dopamine is what generates feelings of pleasure in our brain. In addition to dopamine causing

feelings of pleasure, other areas of the brain associate these feelings with the opiate used, which gets created into lasting memories. These memories can lead to future cravings, potentially causing an individual to use the medication more than the prescribed dose (Kosten et al., 2002).

NEUROLOGICAL IMPLICATIONS OF OPIOID USE

The amygdala is an essential brain structure that regulates emotional responses. The central nucleus of the amygdala is crucial in the control of the emotional aspects in chronic pain and the learning process of associating a particular stimulus, in this case, the opiate, with reward association. "[T]he central nucleus of the amygdala is the part of the brain that focalizes emotional stimuli associated with chronic pain and addictive opioids," which provides an appropriate neural pathway to draw connections between opioids medications and their continued usage. (Zhang et al., 2014). Additionally, in a study done by Dr. Zhi Zhang and colleagues, it was shown that the use of opioids over time could cause changes in the synaptic plasticity of neurons, which can remain in the brain regardless of opioids being present or not. As an individual ingests opioid medications over a period of time, different areas of the brain are affected in various ways. In a recent study conducted by Dr. Jaymin Upadhyay and colleagues, it was shown that prescription opioid-dependent patients showed evidence of a specific structural abnormality in the neural reward-processing network present in the brain. (Younger et al.,2011). When compared to ten age-matched controls, the researchers found decreased gray matter volume in the bilateral amygdala.

The amygdala is crucial in reward processing, and an essential structure is known to underlie opioid-related addiction, dependence, and tolerance. The results of this study concluded that opioid exposure has an extensive range of effects on the amygdala, some of which include a

decrease in sensitivity of the mu-opioid receptor, modified GABAA receptor functioning, and altered glutamate receptor targeting (Younger et al.,2011). While mu-opioid receptor sensitivity is a topic that has previously been discussed, the GABAA and glutamate receptors are also a critical part of understanding the opioid epidemic as a whole. GABA is the major inhibitory neurotransmitter in the brain, and glutamate is the major excitatory neurotransmitter in the brain. While there are many ways opioids interact with the body, "data suggests opioids exert their excitatory action in the brain indirectly by inhibiting the release of GABA" (Kalyuzhny et al., 2000). By indirectly targeting these receptors, opioid medications can cause irreversible damage to the brain. Results of the study done by Dr. Upadhyay and colleagues showed that in the patient group, there was a significant reduction in the functionality of the anterior insula, nucleus accumbens, and amygdala. Once the results of the study were analyzed, there was a strong correlation with a longer duration of opioid usage and more significant changes in functional connectivity in the afferent and efferent pathways of the amygdala.

In addition to functionality changes in different areas of the brain, recent studies have shown prolonged or repeated exposure to a drug of abuse, such as an opioid, causes structural changes in specific neuronal cells that can remain even after the drug is discontinued. In the case of opiates, repeated exposure can decrease the size of dendrites and soma of neurons in the VTA. The consequences of these neuronal changes are mostly unknown, but these changes could result in a down-regulation of dopamine activity, which can potentially contribute to the anxiety and restlessness associated with opiate withdrawal. Furthermore, chronic exposure to opioid medications can also reduce the regeneration of new neurons in the adult hippocampus, causing further complications (Nestler, 2001). The effects that this has on the functional significance of the hippocampus is still not completely understood, but due to the role the hippocampus plays in

learning and memory, long-term opioid usage could potentially cause changes in these cognitive processes. These findings suggest that the continued use of opioid medications is associated with structural and functional changes in the brain regions associated with impulse control, reward, and motivational functions.

OPIOID DEPENDENCE VS. ADDICTION

While it is known that the prolonged usage of opiates results in tolerance to the medication, differences in the genetic makeup of individuals can play a role in how tolerance to the opioid will manifest. Tolerance can be defined as "the need to increase the dose to achieve the same effect," and can develop for both the euphoric effects that an opiate produces as well as the analgesic effects. (Ballantyne et al.,2012). Numerous studies have shown that tolerance to different opiates will manifest at different rates, a phenomenon that is now called selective tolerance. For example, "tolerance to nausea, vomiting, sedation, euphoria, and respiratory depression occurs rapidly, but there is minimal development of tolerance to constipation and miosis." These findings suggest receptor-related differences in the development of tolerance. Additionally, it has been shown that the administration of benzodiazepines, in conjunction with an opiate, speeds up the development of tolerance. (Freye & Latasch, 2003). This change is likely due to the significant reduction in the secretion of GABA, a neurotransmitter that reduces the overall inhibitory effects of the nervous system, increasing analgesic effects of the drug.

Furthermore, it has been suggested that when using higher potency opiates, which produce more significant effects when bound to receptors, fewer receptors are needed to produce sufficient analgesic effects. Receptor downregulation and desensitization have been observed in individuals who use opioids for prolonged periods and have shown to play a critical role in the

development of tolerance and dependence (Harrison et al., 1998). Due to the decrease in receptors needed for higher potency opiates, tolerance is less likely to manifest. Once tolerance to an opiate has developed, an increase in the dose of the medication may be necessary to produce similar analgesic effects.

While most individuals do not take an opiate for the first time thinking they will develop an addiction, addiction can occur over time. There is no concrete definition as to why this happens, but it can be concluded that the chemical makeup of the opiate and the effect it has on the different pathways of the brain play a large part in it. Addiction and dependence are not synonymous terms, but they both stem from the same fundamental principles. From a biological perspective, opioid addiction can be explained by neurological variations that arise when exogenous opioids are used. Dependence can be defined as the physiological response an increase in tolerance or to the withdrawal of a drug (Ballantyne et al., 2012). Dependence can manifest as withdrawal symptoms, such as anxiety, chills, and insomnia, which can occur after the sudden tapering down of opioid usage or complete termination of the opioid. When understanding how addiction and dependence differ, it needs to be understood that addiction is defined as persistent, atypical "opioid-seeking behaviors" that result in irreversible changes in brain structure and function (Ballantyne et al., 2012). There are different theories of addiction, but the Goldstein hypothesis presents the most recognizable link between the mu-receptor variations and opioid addiction. This hypothesis states that in addicts, the amount of endogenous opioid present may be too low, causing the addict to attempt to restore this deficiency by increasing the use of external opioids. This leads us to believe that an inadequate surface expression or inadequate activity of the mu-opioid receptor may predispose an individual to (opiate) addiction (Goldstein, 1994).

Additionally, numerous genetic variations can cause polymorphisms in the coding region of the mu-opioid receptor. These polymorphisms can lead to the upregulation or downregulation of the gene encoding for the receptor. Furthermore, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tolerance and withdrawal (physical dependence) that is developed during medical drug treatment are excluded from diagnostic criteria for substance use disorder. Therefore, any tolerance or withdrawal symptoms that manifest during treatment are not taken into consideration, and the diagnosis is solely based on aberrant or drug-seeking behaviors (Ballantyne et al., 2012)**.** For individuals who are treated with opioid medications long term, addictive behaviors may surface when the opioid is suddenly stopped, or the dosage is reduced due to the alterations in brain structure that arise from the long-term usage of opioid medications. While there is a substantial amount of literature on the effects of long-term opioid exposure on the brain, the effects of their short-term usage are still mostly unknown.

INTERACTIONS WITH OTHER SUBSTANCES

With the increasing rate of opioid medications being prescribed, there has also been an increase in the amount of new synthetic opioid analogs being created. While these new medications are very potent in their analgesic effects, they can cause fatal side effects when combined with other substances. In fact, "[f]entanyl analogs are more potent than fentanyl, which is 50 times more potent than morphine" (Perez-Mana et al.,2018). Additionally, some fentanyl analogs have a much longer duration of action, which can cause more severe interactions with other substances. When understanding how opiates interact with other substances, it is crucial to understand how these medications are metabolized in the human body and how external substances, such as opioids, effect this metabolism. When an opiate is

administered, it is metabolized into active and non-active components. Taking a second substance can inhibit or accelerate the metabolism, resulting in an increase or decrease in the plasma concentration of the opiate. The increase in plasma concentration of a substance can lead to an increase in the therapeutic effects of the drug causing toxic effects. These drug-drug interactions will manifest differently in every individual, but they are divided into two main groups: pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions refer to drug interactions that influence each other's effects directly. These interactions are usually synergistic, meaning "the effect of the two drugs taken together is greater than the sum of their separate effect at the same doses." When considering pharmacodynamic interactions, opioid medications and their analogs interact with other central nervous system depressant drugs such as antihistamines, benzodiazepines, and barbiturates, causing an increase in their therapeutic effects. Pharmacokinetic interactions occur when a second drug "interferes with the absorption, distribution, metabolism, or excretion" of the first opioid taken (Perez-Mana et al.,2018). Pharmacokinetic interactions can be seen with opioids and the administration of naloxone, a non-selective opioid antagonist. Administration of an opioid antagonist such as naloxone can help reverse the effects of an opioid by acting as a competitive inhibitor of the mu-opioid receptor, binding to the receptor with a higher affinity than the opioid.

Due to the differences in the chemical diversity of these products, their exponential increase can complicate the proper absorption of these substances. While opioid analogs like fentanyl are excellent sources of pain relief, their potency and prolonged duration of action can increase the risk of severe interactions and potential toxicity. With the growing use of potent opioid analogs such as fentanyl, there has also been an increase in the amount of illicitly manufactured fentanyl, causing a spike in overdose deaths. (Prekupec et al., 2017). Substances

most commonly involved in these cases of "poly-intoxication are antidepressants, antihistamines, antipsychotics, benzodiazepines, analgesics, anesthetics, psychostimulants, other opioids, alcohol, and illegal drugs of abuse" (Perez-Mana et al.,2018).

Serotonin reuptake inhibitors, a class of antidepressant medication, can interact with opioid medications causing a significant increase in the plasma concentrations of the opiate. This increase is due to the effects of serotonin reuptake inhibitors and on Cytochrome P450 (CYP 450), an enzyme system that aids in the metabolism of opioids. It has been shown that both fluoxetine and fluvoxamine have been considered for potential drug interactions with other opioids such as methadone and buprenorphine. (McCance-Katz et al.,2010). These antidepressants were shown to inhibit CYP450, resulting in decreased metabolism of methadone and buprenorphine. Fluoxetine was not associated with a clinically significant increase in methadone concentrations, but fluvoxamine has been reported to show marked increases in plasma methadone concentrations. Furthermore, when discontinued, fluvoxamine was correlated with the onset of opioid withdrawal. Subsequent opiate withdrawal is a risk associated with the administration of a medication that inhibits methadone metabolism, and discontinuation of the accompanying medication results in healthy methadone metabolism. Additional serotonin reuptake inhibitors that have shown to interact with methadone to some degree are sertraline, citalopram, duloxetine, and amitriptyline.

Anxiolytic medications such as benzodiazepines and sedative-hypnotics share some pharmacological properties such as sedation and altered cognition with methadone and buprenorphine. (McCance-Katz et al.,2010). When taken in conjunction with opioids, benzodiazepines act synergistically with opioids by facilitating inhibition at the GABA receptor and decreasing the effects of glutamate at its target receptor, leading to an increased risk of fatal

respiratory depression through agonist actions at the mu-opioid receptors in the medullary respiratory center. Diazepam and alprazolam, two commonly used anxiolytic medications, were also shown to cause fatal interactions with opiates such as methadone and buprenorphine; the ingestion of these two medications together resulted in fatalities in the most severe cases. (McCance-Katz et al.,2010). Reported fatalities due to the co-ingestion of alprazolam and methadone were due to pharmacodynamic interactions between the two, which was shown to increase the toxicity of the substances, suggesting exercising caution when prescribing the two simultaneously. Similar interactions occur between alcohol and opioid medications as those between anxiolytic medications and opioids.

Antihistamine medications, which are commonly prescribed for allergies, have also been shown to interact with certain opioid medications due to their effects on the CYP450 enzyme system. This enzyme system contributes to the metabolism of some antihistamine medications such as promethazine, diphenhydramine, and chlorpheniramine. Promethazine and diphenhydramine were shown to inhibit the CYP450 enzyme system, resulting in the decreased metabolism of these drugs, causing them to stay in the body longer than usual, increasing the risk of an interaction with an opioid. "These interactions may result from the pharmacokinetic interactions as well as synergistic effects of opioid use in combination with an antihistamine medication" (McCance-Katz et al.,2010). While there is not sufficient literature on these drugs and how they may interact with opiates, these medications have similar characteristics as those shown to cause interactions with opioids.

There have been minimal reports of antipsychotic medications interacting with opioids due to the differences in the pathways used for the metabolism of these drugs. Antipsychotics such as risperidone, clozapine, aripiprazole, olanzapine, and ziprasidone have not been shown to

cause interactions with opioid medications. Some side effects may occur as a result of increased sedation or cognitive dysfunction but are only seen when the two medications are given simultaneously. (McCance-Katz et al.,2010). While older antipsychotic medications have not shown any interactions with opioids, a newer atypical antipsychotic medication, quetiapine has the potential to increase plasma methadone concentrations when given with opioids such as methadone. Studies have shown that quetiapine is predominantly metabolized by the cytochrome P450 enzyme system, the same pathway that is used for metabolizing opioids (DeVane & Nemeroff, 2001). Although there have not been any reports of increased plasma methadone levels in individuals treated with quetiapine, the mechanism of methadone clearance could be of importance.

Anticonvulsant medications, a class of drugs commonly used to treat seizure disorders or mental illnesses, have been shown to cause significant drug interactions with opioids. Most anticonvulsant medications are shown to induce the cytochrome P450 enzyme system. During the metabolism of these drugs, the CYP450 system is induced and hydroxylates or conjugates the anticonvulsant, breaking it down into different chemical metabolites. The induction of this enzyme system leads to a higher clearance of the anticonvulsant medication and other medications metabolized by this system, such as methadone. Due to this, larger doses of methadone are required in patients treated with anticonvulsant medication. It has been shown that carbamazepine, phenytoin, and phenobarbital have been associated with opioid withdrawal when administered to methadone-maintained patients (Bromfield et al.,2006). Additionally, newer anticonvulsant medications such as oxcarbazepine and lamotrigine have not been shown to interact with opioids (McCance-Katz et al.,2010).

Psychostimulants, which are commonly prescribed for attention deficit hyperactivity disorder, have not been shown to produce interactions with opioid medications. However, drugs of abuse that also fall under the stimulant category, such as cocaine, were shown to deplete buprenorphine concentrations. These interactions may be a result of cocaine inducing buprenorphine metabolism through CYP450. Another possible way this occurs is due to the vasoconstrictive effects of cocaine. Buprenorphine administered through sublingual routes is not absorbed appropriately as a result of the vasoconstriction caused by cocaine. (McCance-Katz et al.,2010). Methamphetamine, another drug of abuse that falls under the stimulant category, has not been shown to interact with opioid medications.

While it has been shown that opioid medications are a great source of pain relief, they can also cause severe interactions when taken simultaneously with other substances. Most patients who are prescribed opioid medications for pain management are prescribed a combination of other medications as well. These combinations generally imply a higher risk of drug interactions that can cause differences in the therapeutic effects of the drug (Solhaug & Molden, 2017). Research has shown that some opioid medications inhibit the gastrointestinal system and can consequently decrease the absorption of other substances. Additionally, some opioids can act synergistically with other medications that have analgesic or sedative effects, resulting in a significant increase in these effects. While we know that drug interactions due to pharmacokinetic interactions affect drug transport through the membrane along with the Cytochrome P450 (CYP 450) enzyme system, our knowledge regarding the role of this enzyme system is still minimal. Although we cannot precisely predict how an individual will respond to the effects caused by opioids interacting with other medications, it is crucial to understand what

potential interactions exist between opioids and other substances when prescribing these medications to patients. (Heiskanen& Kalso, 2012).

POTENTIAL COMPLICATIONS FROM OPIOID USAGE

When trying to manage pain by using opioid medications, they can act peripherally or centrally. Opioids act on the peripheral sources of pain by reducing the stimuli that cause pain sensations, or on the central sources by concealing the perception of pain (Solhaug & Molden, 2017). Individual differences can cause discrepancies in their analgesic properties, and the tolerability of opioids can vary due to factors such as age, weight, gender, and organ function. Additionally, genetic variabilities can cause differences in their clinical effects and how an individual will respond to the medication over time. Genetic variations that change the distribution of the opioid throughout the body are known as "genetic causes for changed pharmacokinetics of the opioid" administered (Lötsch et al., 2012). Such polymorphisms can affect the function of the membrane transporters, modifying the bioavailability of the opioid in the body. Furthermore, these polymorphisms can also affect the distribution and elimination of the opioid administered. While the adverse effects of this class of polymorphisms are minimal, the opioid quantity administered may not be sufficient to produce the desired analgesic effects. The effects of this can potentially be avoided by altering the dosage to meet the needs of the individual. Once an opioid has been administered, it is broken down into different metabolites and travel through the bloodstream to its target receptor sites; at the receptor, the opioid will produce its desired effects. Differences in the genetic makeup of an individual can affect the pharmacodynamics of the opioid. Pharmacogenetics can affect the movement of the opioid throughout the body, as well as the opioids mechanism of action and effects on an individual.

Pain perception can vary greatly in different individuals, and while opioids are generally very effective in their analgesic properties, they can cause several side effects. Although there can be variability in how these side effects will manifest, we can say that constipation, nausea and vomiting, sedation, and respiratory depression remain among the most common. In addition to these common side effects, it has been noted that bladder dysfunction, psychomotor changes, cardiovascular effects, and hormonal changes have also been seen in patients receiving opioid therapy. While we cannot predict which patients will experience specific side effects, if any, recent findings have given us better insight into what can be expected.

Constipation is one of the most common side effects associated with opioid usage, "occurring in 40% to 95% of patients treated with opioids". Although constipation can often be dismissed as a minor side effect, the long-term consequences of constipation can result in significant adverse effects for the patient. This side effect is due to opioids acting on the mu-opioid receptor in the gastrointestinal tract and their effects on the CNS, which are thought to slow gut motility. Additionally, opioids act on the enteric nervous system to limit gut motility peripherally. Unlike some opioid side effects, opioid-induced constipation is not one that is likely to improve over time. While there are plenty of stool softeners available that can be prescribed to patients experiencing opioid-induced constipation, a "novel approach" to managing this side effect includes blocking opioid receptors in the peripheral gastrointestinal tract with opioid receptor antagonists (Benyamin et al., 2008). Two new mu-receptor agonists, methylnaltrexone and avimopan, are currently under investigation for opioid-induced constipation. Methylnaltrexone, a naloxone derivative, works by blocking the peripheral actions of opioids while maintaining the analgesic effects they have on the central nervous system.

Avimopan, a selective mu-receptor antagonist, is still under review but has still not shown efficacy with opioid-induced constipation.

While uncommon with most oral opioid analgesic medications, bladder dysfunction can be a side effect of opioid usage. Opioid-induced bladder dysfunction is commonly a side effect in postoperative patients but can be challenging to assess due to multiple other factors that can potentially cause this as well. Urinary retention is more likely to occur when an opioid analgesic is given via injection, intravenously, or intramuscularly, which is thought to be due to a decrease in detrusor muscle tone and a decreased force of contraction that is caused by opioid medications. Additionally, opioids can decrease the sensation of fullness and urge to void, inhibiting the void reflex, causing urinary retention. A study done by Rosow and collogues showed that opioid-induced bladder changes are partly due to peripheral effects of opioid medications and can be reversed by methylnaltrexone. In addition to bladder dysfunction, psychomotor performance changes may also be a side effect of opioid therapy. This effect is likely due to the sedative effect caused by opioids, making some activities of daily living tasks very challenging. When initially starting opioid therapy, it is common that patients experience difficulty with psychomotor tasks. While changes in psychomotor abilities can be a severe side effect of opioid therapy, it is also one of the side effects that subsides with long- term opioid therapy. Furthermore, it has been shown that patients with chronic pain on a fixed opioid analgesic therapy were capable of operating automobiles safely during the daytime (Schisler et al., 2012). Additionally, in a study done by Fishbain and colleagues, opioid-dependent patients, who have some level of opioid tolerance, showed no impairment of psychomotor abilities, even immediately following a dose of the opioid (Fishbain et al., 2003).

In addition to the more common side effects of opioids, such as constipation and bladder dysfunction, opioid analgesics can also cause cardiovascular effects. While not very common, morphine has been associated with some cardiovascular side effects when administered long term due to histamine release, resulting in vasodilation and hypotension (Brunton et al., 2006). Additionally, parasympathetic stimulation by opioids may contribute to bradycardia that may be experienced during opioid therapy and a severe syndrome of QT prolongation known as torsade des pointes. This side effect is one that is seen most commonly in patients who are receiving methadone assisted treatment, a synthetic opioid used in patients who are battling narcotic drug addiction. While we are not able to accurately predict how many patients will experience bradycardia or torsade des pointes, due to the severity of these side effects, repeated surface EKGs are recommended throughout methadone therapy (Benyamin et al., 2008). Opioid-induced hormonal changes can occur with oral, intravenous, transdermal, and intrathecal administration. The hormonal effects of opioids can affect both men and women equally and can act on a variety of hormones, including but not limited to testosterone, estrogen, luteinizing hormone, gonadotrophin-releasing hormone, and cortisol. While there are several hormones affected, there is an emphasis on androgen hormones due to their "symptomatic side effects" of opioid therapy. Men who are prescribed opioid medications suffer from several side effects, including "sexual dysfunction, depression, and decreased energy levels," due to the androgen hormones effected by opioid usage (Benyamin et al., 2008). Women are expected to experience similar hormonally linked side effects as well as potentially experiencing reduced bone mineral density, which may be linked to reduced estrogen levels caused by opioid therapy.

Opioid analgesics have proven to be very useful for pain relief, but they also can cause a number of side effects. Some complications such as nausea and vomiting, sedation, and

constipation do lessen after prolonged exposure to the opioid. Other side effects, such as cardiovascular changes and hormonal changes are unlikely to subside throughout the duration of opioid therapy, potentially causing long-term physiological changes. Cardiovascular changes can also lead to further, more severe complications due to the vasodilatation and QT prolongation. Additionally, the symptomatic side effects caused by opioid-induced hormonal changes such as reduced bone mineral density are unlikely to be reversible, causing irreversible changes in the patient's body.

CONCLUSION

The opioid epidemic is a severe issue impacting individuals all over the world. While opioid analgesics are an efficient source of pain relief, they can exhibit a number of side effects depending on the individual. When analyzed, individuals who are prescribed opioids for long term therapy show irreversible changes in brain structure, specifically in the regions responsible for learning and memory. Prescription opioid-dependent patients also show evidence of structural abnormalities in the amygdala, the area responsible for reward processing in the brain. When compared to age-matched individuals, opioid-dependent patients showed decreased gray matter volume in the bilateral amygdala, along with functional connectivity changes in the afferent and efferent pathways of the amygdala. Additionally, prolonged exposure to opioids can also lead to decreased sensitivity in the mu-opioid receptor, modified GABAA receptor functioning, and altered glutamate receptor targeting. Long term dependence on opioids for their analgesic effects can also lead to the development of tolerance or even addiction in some patients. While we are not able to foresee which patients will become tolerant to these medications, numerous studies have shown that tolerance to different opiates will manifest at

different rates. Once tolerance to an opiate has developed, an increase in the dose of the medication may be necessary to produce similar analgesic effects.

Another potential area for concern when considering opioid therapy is the increased risk for drug-drug interactions. While several interactions can manifest when taking opioid medications, these interactions are divided into two groups. Pharmacokinetic interactions, which refer to interactions that affect the absorption, metabolism, and excretion of the first drug taken and pharmacodynamic, which influence each other's effects directly. Pharmacodynamic interactions with opioids are frequent when taking additional central nervous system depressants such as antihistamines, benzodiazepines, and barbiturates, causing a resultant increase in the therapeutic effects of the opioid administered. It has been shown that a second substance can accelerate the metabolism, increasing the plasma concentration of the drug, potentially causing toxic effects, an occurrence now referred to as poly- intoxication. Additionally, when adding medications that are metabolized by the CYP450 enzyme system may cause variances in the metabolism of the opioid taken. For example, the second substance can also inhibit the metabolism of the opioid administered, causing the patient to feel insufficient pain relief. This can lead to very dangerous, potentially fatal overdoses if the patient self- administers more of the opioid. While proper patient education and strict monitoring by the patients' physician can help minimize these interactions, it is still something that needs to be taken into consideration when putting a patient on opioid therapy for long term pain relief.

Opioid analgesics are an up-and-coming class of medications but require strict monitoring when administered. Due to the subjective nature of pain, it is difficult to assess which patients should be prescribed potent analgesics such as opioid medications, but they should be prescribed with extreme caution regardless. We are still very unsure of both the short and long-term

implications that opioid therapy entails, and it is essential that we thoroughly examine all other options before beginning opioid therapy. The opioid epidemic is a widespread issue that affects multiple parts of our healthcare system. Hopefully, as time progresses and more research is done, we can get a better understanding of the epidemic as a whole and what we can do to help slow the progression.

References

Backmund, M., Schuetz, C., Meyer, K., Edlin, B. R., & Reimer, J. (2009). The risk of emergency room treatment due to overdose in injection drug users. *Journal of Addictive Diseases, 28*(1), 68-73. doi:10.1080/10550880802545192

Ballantyne, J. C. (2007). Opioid analgesia: Perspectives on right use and utility. *Pain Physician, 10*(3), 479-491.

Ballantyne, J. C., Sullivan, M. D., & Kolodny, A. (2012). Opioid dependence vs addiction: A distinction without a difference? *Archives of Internal Medicine, 172*(17), 1342-1343. doi:10.1001/archinternmed.2012.3212

Bechara, A., Nader, K., & Van Der Kooy, D. (1998). A two-separate-motivational-systems hypothesis of opioid addiction. *Pharmacology Biochemistry and Behavior, 59*(1), 1-17. doi:10.1016/S0091-3057(97)00047-6

Behrends, C. N., Paone, D., Nolan, M. L., Tuazon, E., Murphy, S. M., Kapadia, S. N., . . . Schackman, B. R. (2019). Estimated impact of supervised injection facilities on overdose fatalities and healthcare costs in new york city. *Journal of Substance Abuse Treatment, 106*, 79-88. doi:10.1016/j.jsat.2019.08.010

Benyamin, R., Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., . . . Vallejo, R. (2008). Opioid complications and side effects. *Pain Physician, 11*(2 Suppl), 105.

Birnbaum, H. G., White, A. G., Reynolds, J. L., Greenberg, P. E., Zhang, M., Vallow, S., . . . Katz, N. P. (2006). Estimated costs of prescription opioid analgesic abuse in the united states in 2001: A societal perspective. *The Clinical Journal of Pain, 22*(8), 667-676. doi:10.1097/01.ajp.0000210915.80417.cf

Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal costs of prescription opioid abuse, dependence, and misuse in the united states. *Pain Medicine, 12*(4), 657-667. doi:10.1111/j.1526-4637.2011.01075.x

Boscarino, J. A., Hoffman, S. N., & Han, J. J. (2015). Opioid-use disorder among patients on long-term opioid therapy: Impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Substance Abuse and Rehabilitation, 6*, 83-91. doi:10.2147/SAR.S85667

Brett, J. (2015). Concerns about quetiapine. *Australian Prescriber, 38*(3), 95-97. doi:10.18773/austprescr.2015.032

Bromfield, E. B., Cavazos, J. E., & Sirven, J. I. (2006). *Neuropharmacology of antiepileptic drugs* American Epilepsy Society. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK2513/

Christie, M. J. (2008). Cellular neuroadaptations to chronic opioids: Tolerance, withdrawal and addiction. *British Journal of Pharmacology, 154*(2), 384-396. doi:10.1038/bjp.2008.100

Collins, A. B., Boyd, J., Mayer, S., Fowler, A., Kennedy, M. C., Bluthenthal, R. N., . . . McNeil, R. (2019). Policing space in the overdose crisis: A rapid ethnographic study of the impact of

law enforcement practices on the effectiveness of overdose prevention sites. *The International Journal on Drug Policy,* doi:10.1016/j.drugpo.2019.08.002

DeVane, C. L., & Nemeroff, C. B. (2001). Clinical pharmacokinetics of quetiapine: An atypical antipsychotic. *Clinical Pharmacokinetics, 40*(7), 509-522. doi:10.2165/00003088-200140070-00003

Dowell, D., Noonan, R. K., & Houry, D. (2017). Underlying factors in drug overdose deaths. *Jama, 318*(23), 2295-2296. doi:10.1001/jama.2017.15971

Fishbain, D. A., Cutler, R. B., Rosomoff, H. L., & Rosomoff, R. S. (2003). Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. *Journal of Pain and Symptom Management, 25*(6), 559-577. doi:10.1016/s0885-3924(03)00176-3

Florence, C., Luo, F., Xu, L., & Zhou, C. (2016). The economic burden of prescription opioid overdose, abuse and dependence in the united states, 2013. *Medical Care, 54*(10), 901-906. doi:10.1097/MLR.0000000000000625

Freye, E., & Latasch, L. (2003). [Development of opioid tolerance -- molecular mechanisms and clinical consequences]. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie: AINS, 38*(1), 14-26. doi:10.1055/s-2003-36558

Frisoni, P., Bacchio, E., Bilel, S., Talarico, A., Gaudio, R. M., Barbieri, M., . . . Marti, M. (2018). Novel synthetic opioids: The pathologist's point of view. *Brain Sciences, 8*(9) doi:10.3390/brainsci8090170

Hansen, R. N., Oster, G., Edelsberg, J., Woody, G. E., & Sullivan, S. D. (2011). Economic costs of nonmedical use of prescription opioids. *The Clinical Journal of Pain, 27*(3), 194. doi:10.1097/AJP.0b013e3181ff04ca

Harrison, L. M., Kastin, A. J., & Zadina, J. E. (1998). Opiate tolerance and dependence: Receptors, G-proteins, and antiopiates. *Peptides, 19*(9), 1603-1630. doi:10.1016/s0196-9781(98)00126-0

Hedegaard, H., Bastian, B. A., Trinidad, J. P., Spencer, M., & Warner, M. (2018). Drugs most frequently involved in drug overdose deaths: United states, 2011-2016. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 67*(9), 1-14.

Heiskanen, T., & Kalso, E. (2012). Non-analgesic effects of opioids: Interactions between opioids and other drugs. *Current Pharmaceutical Design, 18*(37), 6079-6089. doi:10.2174/138161212803582423

Hser, Y., Evans, E., Grella, C., Ling, W., & Anglin, D. (2015). Long-term course of opioid addiction. *Harvard Review of Psychiatry, 23*(2), 76–89. doi:10.1097/HRP.0000000000000052

Kalyuzhny, A. E., Dooyema, J., & Wessendorf, M. W. (2000). Opioid- and GABA(A)-receptors are co-expressed by neurons in rat brain. *Neuroreport, 11*(12), 2625-2628. doi:10.1097/00001756-200008210-00004

Kerr, T., Mitra, S., Kennedy, M. C., & McNeil, R. (2017). Supervised injection facilities in canada: Past, present, and future. *Harm Reduction Journal, 14*(1), 28. doi:10.1186/s12954-017-0154-1

Kirson, N. Y., Shei, A., Rice, J. B., Enloe, C. J., Bodnar, K., Birnbaum, H. G., . . . Ben-Joseph, R. (2015). The burden of undiagnosed opioid abuse among commercially insured individuals. *Pain Medicine (Malden, Mass.), 16*(7), 1325-1332. doi:10.1111/pme.12768

Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: Implications for treatment. *Science & Practice Perspectives, 1*(1), 13-20. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18567959

Lindsey, W. T., Stewart, D., & Childress, D. (2012). Drug interactions between common illicit drugs and prescription therapies. *The American Journal of Drug and Alcohol Abuse, 38*(4), 334-343. doi:10.3109/00952990.2011.643997

Lintzeris, N., Mitchell, T. B., Bond, A. J., Nestor, L., & Strang, J. (2007a). Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug and Alcohol Dependence, 91*(2-3), 187-194. doi:10.1016/j.drugalcdep.2007.05.019

Lintzeris, N., Mitchell, T. B., Bond, A. J., Nestor, L., & Strang, J. (2007b). Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug and Alcohol Dependence, 91*(2-3), 187-194. doi:10.1016/j.drugalcdep.2007.05.019

Lötsch, J., Skarke, C., Liefhold, J., & Geisslinger, G. (2004). Genetic predictors of the clinical response to opioid analgesics: Clinical utility and future perspectives. *Clinical Pharmacokinetics, 43*(14), 983-1013. doi:10.2165/00003088-200443140-00003

Lovrecic, B., Lovrecic, M., Gabrovec, B., Carli, M., Pacini, M., Maremmani, A. G. I., & Maremmani, I. (2019). Non-medical use of novel synthetic opioids: A new challenge to public health. *International Journal of Environmental Research and Public Health, 16*(2) doi:10.3390/ijerph16020177

Lüscher, C., & Malenka, R. (2011). Drug-evoked synaptic plasticity in addiction: From molecular changes to circuit remodeling. *Neuron, 69*(4), 650-663. doi:10.1016/j.neuron.2011.01.017

Mayer, P., & Höllt, V. (2006). Pharmacogenetics of opioid receptors and addiction. *Pharmacogenetics and Genomics, 16*(1), 1. doi:10.1097/01.fpc.0000182781.87932.0d

McCance-Katz, E. F., Sullivan, L., & Nallani, S. (2010). Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: A review. *The American Journal on Addictions, 19*(1), 4-16. doi:10.1111/j.1521-0391.2009.00005.x

Merlo, L. J., & Gold, M. S. (2008). Prescription opioid abuse and dependence among physicians: Hypotheses and treatment. *Harvard Review of Psychiatry, 16*(3), 181-194. doi:10.1080/10673220802160316

Miller, N. S., Belkin, B. M., & Gold, M. S. (1991). Alcohol and drug dependence among the elderly: Epidemiology, diagnosis, and treatment. *Comprehensive Psychiatry, 32*(2), 153-165. doi:10.1016/0010-440x(91)90008-z

Nelson, L. S., Juurlink, D. N., & Perrone, J. (2015). Addressing the opioid epidemic. *Jama, 314*(14), 1453-1454. doi:10.1001/jama.2015.12397

Nestler, E. J. (2001). Molecular basis of long-term plasticity underlying addiction. *Nature Reviews Neuroscience, 2*(2), 119-128. doi:10.1038/35053570

Oderda, G. M., Lake, J., Rüdell, K., Roland, C. L., & Masters, E. T. (2015). Economic burden of prescription opioid misuse and abuse: A systematic review. *Journal of Pain & Palliative Care Pharmacotherapy, 29*(4), 388-400. doi:10.3109/15360288.2015.1101641

Pérez-Mañá, C., Papaseit, E., Fonseca, F., Farré, A., Torrens, M., & Farré, M. (2018). Drug interactions with new synthetic opioids. *Frontiers in Pharmacology, 9*, 1145. doi:10.3389/fphar.2018.01145

Perron, B. E., Bohnert, A. S. B., Monsell, S. E., Vaughn, M. G., Epperson, M., & Howard, M. O. (2011). Patterns and correlates of drug-related ED visits: Results from a national survey. *The American Journal of Emergency Medicine, 29*(7), 704-710. doi:10.1016/j.ajem.2010.01.044

Prekupec, M. P., Mansky, P. A., & Baumann, M. H. (2017). Misuse of novel synthetic opioids: A deadly new trend. *Journal of Addiction Medicine, 11*(4), 256-265. doi:10.1097/ADM.0000000000000324

Raghavan, S., Harvey, A. D., & Humble, S. R. (2011). New opioid side effects and implications for long-term therapy. *Trends in Anaesthesia and Critical Care, 1*(1), 18-21. doi:10.1016/j.cacc.2010.06.003

Rice, J. B., Kirson, N. Y., Shei, A., Enloe, C. J., Cummings, A. K., Birnbaum, H. G., . . . Ben-Joseph, R. (2014). The economic burden of diagnosed opioid abuse among commercially insured individuals. *Postgraduate Medicine, 126*(4), 53-58. doi:10.3810/pgm.2014.07.2783

Rosow, C. E., Gomery, P., Chen, T. Y., Stefanovich, P., Stambler, N., & Israel, R. (2007). Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. *Clinical Pharmacology and Therapeutics, 82*(1), 48-53. doi:10.1038/sj.clpt.6100164

Ross, S. M., & Chappel, J. N. (1998). Substance use disorders. difficulties in diagnoses. *The Psychiatric Clinics of North America, 21*(4), 803-828.

Ruan, X. (2007). Drug-related side effects of long-term intrathecal morphine therapy. *Pain Physician, 10*(2), 357-366.

Ruano, G., & Kost, J. A. (2018). Fundamental considerations for genetically-guided pain management with opioids based on CYP2D6 and OPRM1 polymorphisms. *Pain Physician, 21*(6), E611-E621.

Saunders, E., Metcalf, S. A., Walsh, O., Moore, S. K., Meier, A., McLeman, B., . . . Marsch, L. A. (2019). "You can see those concentric rings going out": Emergency personnel's experiences treating overdose and perspectives on policy-level responses to the opioid crisis in new hampshire. *Drug and Alcohol Dependence, 204*, 107555. doi:10.1016/j.drugalcdep.2019.107555

Schisler, R. E., Groninger, H., & Rosielle, D. A. (2012). Counseling patients on side effects and driving when starting opioids #248. *Journal of Palliative Medicine, 15*(4), 484-485. doi:10.1089/jpm.2012.9596

Semenkovich, K., Chockalingam, R., Scherrer, J. F., Panagopoulos, V. N., Lustman, P. J., Ray, J. M., . . . Svrakic, D. M. (2014). Prescription opioid analgesics increase risk of major depression: New evidence, plausible neurobiological mechanisms and management to achieve depression prophylaxis. *Missouri Medicine, 111*(2), 148-154. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6179498/

Shei, A., Rice, J. B., Kirson, N. Y., Bodnar, K., Enloe, C. J., Birnbaum, H. G., . . . Ben-Joseph, R. (2015). Characteristics of high-cost patients diagnosed with opioid abuse. *Journal of Managed Care & Specialty Pharmacy, 21*(10), 902-912. doi:10.18553/jmcp.2015.21.10.902

Solhaug, V., & Molden, E. (2017). Individual variability in clinical effect and tolerability of opioid analgesics - importance of drug interactions and pharmacogenetics. *Scandinavian Journal of Pain, 17*, 193-200. doi:10.1016/j.sjpain.2017.09.009

Stotts, A. L., Dodrill, C. L., & Kosten, T. R. (2009). Opioid dependence treatment: Options in pharmacotherapy. *Expert Opinion on Pharmacotherapy, 10*(11), 1727-1740. doi:10.1517/14656560903037168

Strassels, S. A. (2009). Economic burden of prescription opioid misuse and abuse. *Journal of Managed Care Pharmacy: JMCP, 15*(7), 556-562. doi:10.18553/jmcp.2009.15.7.556

Swegle, J. M., & Logemann, C. (2006). Management of common opioid-induced adverse effects. *American Family Physician, 74*(8), 1347-1354.

Treatment, Institute of Medicine (US) Committee on Federal Regulation of Methadone, Rettig, R. A., & Yarmolinsky, A. (1995). *Pharmacology and medical aspects of methadone treatment* National Academies Press (US). Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK232112/

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., . . . Borsook, D. (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain, 133*(7), 2098-2114. doi:10.1093/brain/awq138

Vallejo, R., de Leon-Casasola, O., & Benyamin, R. (2004). Opioid therapy and immunosuppression: A review. *American Journal of Therapeutics, 11*(5), 354-365. doi:10.1097/01.mjt.0000132250.95650.85

Ventura, L., Carvalho, F., & Dinis-Oliveira, R. J. (2018). Opioids in the frame of new psychoactive substances network: A complex pharmacological and toxicological issue. *Current Molecular Pharmacology, 11*(2), 97-108. doi:10.2174/1874467210666170704110146

Wolfe, S., Bouffard, D. L., & Modesto-Lowe, V. (2016). The opioid crisis and the physician's role in contributing to its resolution: Step one--prevention of overdoses. *Connecticut Medicine, 80*(6), 325-334.

Wu, L., ScD, Swartz, M. S., MD, Wu, Zunyou, PhD, MD, Mannelli, P., MD, Yang, C., PhD, & Blazer, Dan G., PhD, MD. (2012). Alcohol and drug use disorders among adults in emergency department settings in the united states. *Annals of Emergency Medicine, 60*(2), 172-180.e5. doi:10.1016/j.annemergmed.2012.02.003

Wu, L., Woody, G. E., Yang, C., Pan, J., & Blazer, D. G. (2011). Racial/ethnic variations in substance-related disorders among adolescents in the united states. *Archives of General Psychiatry, 68*(11), 1176-1185. doi:10.1001/archgenpsychiatry.2011.120

Younger, J. W., Chu, L. F., D'Arcy, N., Trott, K., Jastrzab, L. E., & Mackey, S. C. (2011). Prescription opioid analgesics rapidly change the human brain. *Pain, 152*(8), 1803-1810. doi:10.1016/j.pain.2011.03.028

ZIAEE, M., HAJIZADEH, R., KHORRAMI, A., SEPEHRVAND, N., MOMTAZ, S., & GHAFFARI, S. (2019). Cardiovascular complications of chronic opium consumption: A narrative review article. *Iranian Journal of Public Health, 48*(12), 2154-2164. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6974854/