DOI: https://doi.org/10.53350/pjmhs22166819

ORIGINAL ARTICLE

Literature Review of the Effects of Long-Term Opioid Use in the Management of Pain

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ABSTRACT

The interminable need to alleviate or sometimes eliminate pain has been perceived by all cultures around the globe for many centuries. The human species has found ways to perform pain management, including oral ingestion of herbs and utilization of procedures believed to have special remedial properties. The current medical practice calls for the application of opioids in the management of pain and this choice spans decades. From a general perspective, medical practitioners globally agree on the appropriateness of opioid use in the management of acute and chronic pain.

Looking at the issue further, a huge controversy arises when the discussion spirals into whether the pros outweigh the cons in the long-term management of pain, especially chronic pain. Opiates belong to a class of drugs that are extracted from the latex sap of the opium poppy (Papaver somniferum) where they occur naturally as alkaloids. The term opioids, also commonly referred to as narcotics (a non-scientific term), is pharmacologically used to refer to artificial or natural chemical compounds that bind to opioid receptors and are antagonized by naloxone. The chemical composition, pharmacodynamics, and pharmacokinetics of opioids are beyond the scope of this review article, whose focus will be mainly aimed at discussing the apparent effects of long-term use of these drugs in pain management.

Keywords: opioids, opiates, narcotics, pain, chronic pain, pain management, long-term use effects

INTRODUCTION

Defining 'Long-Term Opioid Use': A glance at the title of this article, raises an important question. Exactly how long is 'long'? To the general public, long-term use remains subjective and this, therefore, necessitates the need to refer to a medically accepted operational definition that will enable the reader to keep in mind the duration being referenced. The accepted definition of chronic pain is that it lasts for more than three months (explained further in section **1.c.**). Long-term opioid use can be described as receiving a prescribed opioid on half or more of a ninety-day prescription period (Durand et al., 2019). That said, the definition of long-term use refers not only to the number of days a prescribed opioid for pain management is administered, but it is also inclusive of the threshold at which incidentals and expenses of opioid use start to overshadow the benefits. (Summarized in Figure 1.)

Figure 1:

Definition of pain: To understand the effects that come with long-term opioid use in pain management, it is crucial that we first understand pain from a clinical perspective. The most widely accepted definition of pain, by health practitioners around the world and researchers, is from the International Association for the Study of Pain (IASP) (Raja et al., 2020). The IASP currently describes pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage, or described in terms of that damage." This definition has been accepted and adopted by many specialized, nongovernmental (inclusive of WHO) and governmental organizations (Raja et al., 2020).

Chronic pain in context: As the long-term use of opioids is mostly for the amelioration of chronic pain, this kind of pain must be distinguished from others. Chronic pain is pain that stays past the regular time normally taken for health restoration and therefore is not accompanied by the cautionary purpose of physiological nociception (Treede et al., 2015). Pain is said to be chronic if it lasts and/or recurs for more than three months to six months (Benoliel et al., 2010). The severity of pain is classified based on its intensity, its related distress, and the functional impairment it brings with it (Nicholas et al., 2019). There are currently seven major classes of chronic pain (Treede et al., 2015). Table 1 explains them and some of the long-term opioids used in their management.

Table 1:

Type of Chronic Pain	Definition	Opioids used in management
1. Chronic primary pain	Chronic pain in one or more anatomic regions (Treede et al., 2019).	Morphine, oxycodone, fentanyl
2. Chronic cancer pain	Chronic pain caused by cancer (primary tumor and metastases) and cancer treatment (surgery, chemotherapy, radiotherapy, and others) (Bennett et al., 2019).	Morphine, oxycodone, fentanyl, methadone, hydromorphone (Walsh, 1984).
3. Chronic postsurgical and posttraumatic pain	Chronic pain that comes after a surgical procedure or that develops after tissue trauma.	Oxycontin, roxicodone
4. Chronic neuropathic pain	Chronic pain caused by a lesion or disease of the somatosensory nervous system (Scholz et al., 2019).	Oxycodone, hydrocodone
5. Chronic headache and orofacial pain	Headaches and/or orofacial pain that occurs for at least half or more of the days in 3 months or more.	Morphine, oxycodone, oxymorphone, methadone, levorphanol
6. Chronic visceral pain	Chronic pain originating from internal organs of the head, neck, thoracic cavity, abdominal cavity, and/or pelvic cavity (Häuser et al., 2020).	Morphine, oxycodone, oxymorphone
7. Chronic musculoskeletal pain	Chronic pain that comes as a result of the pathophysiology of a disease that directly affects the bones, joints, muscles, and/or their related soft tissue.	Morphine, hydrocodone, oxycodone (Cooper et al., 2017).

Opioid prescriptions: Prescriptions for chronic pain of opioid medications meant to be used over an extended period of time have surged over recent decades. This has gone further to worsen the current opioid crisis (Gottlieb & Woodcock, 2017). While pain remains one of the chief contributors to the deterioration of the quality of life (Hadi et al., 2019), the increased level of prescriptions of opioids has consequently engendered several issues in the panoramic medical field. These issues include and

are not limited to climbing levels of opioid abuse, a surge in the number of prescription-related opioid overdoses, and soaring levels of opioid addiction (Chou et al., 2015).

In addition to all these, the need for better decision-making in the clinical assessment of patients eligible for prescription of these drugs, the exact opioids they will use and their dosages have become very important (Hale et al., 2021). Strict and individualized benefit-risk evaluations for some of these drugs have therefore been necessitated (Gottlieb & Woodcock, 2017). These assessments, as clearly defined and detailed by the Food and Drug Administration make sure that evaluations cover both the effects of the proper and appropriate use of these drugs and the public health effects that come with their inappropriate use (Woodcock & Throckmorton, 2018). Opinionated views, however, describe this as not effective enough to cover the effects of these drugs and solve the ongoing opioid crisis.

Reviewed Effects: The following sections of this article are detailed summaries of reviewed information regarding the effects of the long-term use of opioids, listed in order of clinical significance and occurrence levels. Examples have been given and expounded where necessary.

Abuse and opioid use disorder: A prescribed drug is said to be abused when it is intentionally used for purposes other than the ones it was meant to be used for, or when this drug is used illegally, whether prescribed or bought over the counter. Substance abuse is the excessive use of a drug in a manner that is detrimental to self, society, or both (H. K. Walker et al., 1990). Opioid use disorder is described as a physical or psychological reliance on opioids (Dong et al., 2021). It is characterized by recurrence and is a chronic illness that is associated with high mortality worldwide (Hser et al., 2017).

The biggest debate over whether there is enough data to continue supporting long-term use of opioids, especially for chronic non-cancer pain, is related to the fact that these drugs exhibit the potential to be misused or abused. This potential, as studies show, has a very high likelihood of being actualized. Research from a decade ago showed that the levels of opioid abuse had increased by 300 percent (quadrupled) in the period between 1990 and 2000 in the U.S. (Moorman-Li et al., 2012). From both public health and individual perspectives, the burden of opioid use disorder is immense. In 2016, 26.8 million people around the world were estimated to be living with the disorder (Strang et al., 2020).

The patients themselves, or the relatives or friends who acquire the drugs from them, pursue the euphoric effect of these drugs. Eventually, they end up misusing or abusing them by taking a pharmacologically excessive amount whether in the same or an altered formulation. The long-term use of these drugs only adds fuel to the fire as it ensures the drugs are present for a lengthy period, or a period that is enough to sustain their abuse. Once an opioid is abused, the chances that it will happen again are high.

Continued abuse subsequently leads to the development of opioid use disorder as the individual continues to seek the euphoria and eventually develops dependence on the drug. Therefore, the long-term use of opioids in the management of pain escalates to this unwanted effect in the long run. Research done on the likability and abuse liability of commonly prescribed opioids showed that oral oxycodone has a higher abuse profile than oral morphine and hydrocodone (Wightman et al., 2012).

Addiction and dependence: Another effect of the long-term use of opioids in the management of pain is addiction, which goes hand in hand with dependence, which in turn over time metamorphoses into opioid use disorder. Addiction is described medically as an irrepressible and overwhelming desire to pursue and use a substance or drug. The dependence that is brought forth by addiction becomes very arduous to put the reins on. Furthermore, this dependence relentlessly distresses an individual mentally and physically.

A study done to show the rate of occurrence of addictive behaviors in chronic non-cancer patients that were undergoing long-term opioid pain management analyzed close to 14,000 people. The results revealed that more people (22.6% vs. 11.5%) were using opioids in long-term pain management who showcased addictive behaviors than those using other drugs to manage pain (Højsted et al., 2013). Another study done in 2017 on the burden of illnesses and injuries across the globe found that an estimated 40.5 million people were dependent on opioids (Degenhardt et al., 2019). Opiate dependence, which is brought forth by long-term use, is also comorbid with a range of other mental disorders and often comes laced together with poly-substance abuse and other psychosocial issues (Verthein et al., 2005).

The opiate agonists morphine and fentanyl are the most commonly used in medical locales, produce the most potent effects, and are among the most addictive opioids. Other agonists that are commonly addictive are heroin, oxycodone, methadone, and hydrocodone. The feeling of tranquility and euphoria that accompany these drugs, especially when they are taken in quantities that exceed the prescription amount, is often sought by users leading to compulsive drug-seeking behavior. It is common for patients who have used opioids for long-term pain management to seek heroin, an illegal opioid that actually happens to be low-priced on the streets. Others even go to multiple doctors in an attempt to get more and more prescriptions to quench their addiction needs.

In conclusion, it is therefore beyond a doubt that addiction and dependence are major effects of long-term use of opioids in pain management. Sometimes this spirals down into abuse by individuals who were never even patients initially but managed to gain access to these drugs through friends or family who were using them. The sad thing about this is that this progression often goes unnoticed and undocumented even though it is a major issue in the use of these drugs and of great clinical significance. The situation needs to be promptly and powerfully addressed.

Opioid-Induced hyperalgesia and tolerance: Hyperalgesia is described by the IASP as “increased pain from a stimulus that normally provokes pain” (Yi & Pryzbylkowski, 2015). Opioid-induced hyperalgesia was first documented in the early 19th century. It was recognized that a potent opioid, such as morphine, could eventually result in increased pain in patients. Opioid-induced hyperalgesia is a phenomenon where exposure to opioids, especially on a long-term basis, triggers a state of nociceptive sensitization. It was noted that this phenomenon is distinct and definable, and that it could be the reason why some opioids lost their efficacy in some patients (Marion Lee et al., 2011).

The response that the body expresses is paradoxical in the sense that the patient receiving the opioid that is meant to provide relief of pain instead produces more sensitivity to particular painful stimuli. The pain the patient experiences in opioid-induced hyperalgesia is either similar to, or different from the underlying pain (Marion Lee et al., 2011). Long-term use of opioids is associated with this effect, whose exact pathophysiology is still a medical debate, with theories being discussed regarding the complex nociceptive pathways through which the perception of pain happens.

Through the long-term use or abuse of opioids for their analgesic and gratifying effects respectively, tolerance develops. The tolerance of the human body to opioids has features that show a decline in sensitivity and responsiveness to opioid agonists, for instance, morphine. This often comes accompanied by the need to raise the dosage amounts for anticipated outcomes and effects to be attained (Morgan & Christie, 2011). Numerous studies show that unchanged doses of opioids can indeed provide relief (for weeks to years) from the agony that pain brings. However, this is disproved by practical and clinical practice, as dosage raises to even more than 10 times the original amount in chronic pain are very common (Buntin-Mushock et al., 2005).

Research on the cellular processes through which tolerance to opioids develops is underway even though no conclusive findings have been documented. Long-term use of opioids in the management of pain, therefore, produces hyperalgesia, which in

the long run leaves medical practitioners in a dilemma as the paradox works against their efforts.

Increased risk of overdose and mortality: An overdose describes an amount of a therapeutic drug that is lethal or toxic to the body. If no medical intervention occurs promptly and quickly, drug overdoses can lead to death. With prolonged use of opioids comes the increased potential of their abuse and, therefore, the increased risk of overdose and death. Table 2 below explains the risk factors for opioid overdose, opioid addiction, and both combined.

Table 2:

	Drug-related risk factors	Personal factors
Overdose	1. Co-administration of Benzodiazepines (Oliver et al., 2007). 2. Long-acting prescribed formulation. (methadone, fentanyl patch)	1. Sleep apnea 2. Severe respiratory disability 3. Drug overdose history 4. Renal or hepatic impairment 5. Psychiatric instability 6. Below 30 years or above 65 years of age
Addiction	1. Current ongoing opioid abuse. 2. Long-term opioid use.	1. Adolescence (Windisch & Kreek, 2020). 2. Family or community environments that encourage and facilitate opioid abuse (Webster, 2017). 3. Psychiatric conditions
Overdose and Addiction.	1. Use for duration over 90 days. 2. A dose higher than 100 morphine mg equivalents.	1. Personality disorder 2. Depression (Foley & Schwab-Reese, 2019). 3. Anxiety disorder

Currently, oxycodone and hydrocodone, are the most commonly prescribed opioids and are the leading opioid overdose drugs (Hah et al., 2017). The illegal opioid heroin is also responsible for many deaths through overdose and it is described as the greatest cause of mortality in drug-injecting users in the United States (Green et al., 2008).

In 2014, an estimated 28,000 deaths related to opioid overdose were reported in the U.S. (Mohamadi et al., 2018). A 2016 study reported more than 100,000 opioid overdose-related deaths annually across the globe, with the U.S. experiencing more than 47,000 such deaths in 2017 (Strang et al., 2020). It is clear that the rate of opioid overdose continues to rise (Adewumi et al., 2018). Table 3 below shows the signs and symptoms of opioid overdose.

Table 3: Signs and Symptoms of opioid overdose

1.	Complete loss of consciousness
2.	Confusion
3.	Dilated pupils and watery eyes
4.	Dark lips and fingernails
5.	Shallow or restricted breathing (Palmer & Gautier, 2017)
6.	Vomiting
7.	Intermittent loss of consciousness (Schiller et al., 2017)
8.	Blue and cold skin
9.	Extreme sleepiness
10.	Snoring and gurgling sounds

Gastrointestinal system effects: Patients on long-term opiate therapy experience constipation, which is very prevalent and widely recognized by medical practitioners as one of the unwanted side effects of opiate use (Bell et al., 2009). Therefore, it is common for laxatives and stool softeners to be prescribed together with opioids, especially on long-term therapy, as these serve to treat or alleviate constipation (Swegle & Logemann, 2006). Nausea is also a prevalent side effect. Reports from many studies indicate that an estimated 40% to 45% of patients under chronic opioid therapy experience constipation, while 25% are affected by nausea (Baldini et al., 2012). Opiates also have the potential to cause bloating, abdominal cramping, and vomiting.

Constipation is the most common side effect of long-term opiate therapy, and it is associated with clinically significant psychological distress. It also comes accompanied with an increased prevalence of depression (Dennison et al., 2005). This, therefore, implies that significant attention should be focused on constipation while patients are receiving opioid pain management therapies. To conclude, in the risk-benefit analysis done before a patient is placed on long-term opioid management of pain, the lowered quality of life that comes with the gastrointestinal system effects should be put into consideration (Hjalte et al., 2010).

Respiratory system effects: Long-term opiate use has been associated with many side effects that affect the respiratory system of the body (J. M. Walker et al., 2007; Yue & Guilleminault, 2010). Figure 2 shows some of these side effects.

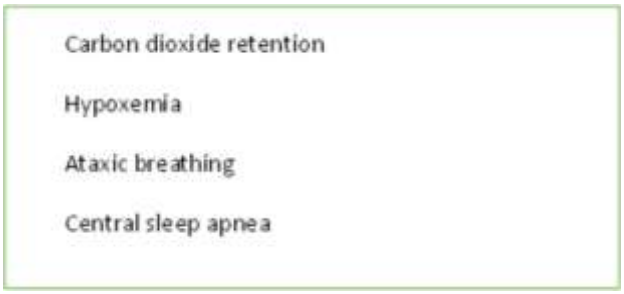

Figure 2: Respiratory side effects of long-term opioid use.

These side effects, all classified as sleep-disordered breathing, have prevalence rates in chronic opioid-therapy patients that go as high as 75% (Webster et al., 2008). This, therefore, means that these side effects come with increased mortality risk. Not enough data have been found to substantiate the morbidity they might harbor, considering that the studies done on this so far represent only a few population percentages and are relatively of microscale (Jennum & Riha, 2009).

Cardiovascular system effects: Long-term use of opioids can indeed have adverse effects on the heart (Corbett et al., 2019). Even though some of the opioid antagonists have no direct negative effects on the cardiovascular system and the contractile properties of the heart, administration of these opioids together with other drugs, for instance, benzodiazepines, is known to be associated with decreased cardiac function (Chen & Ashburn, 2015). Long-term opioid use in pain management can cause a range of cardiovascular side effects, from bradycardia to orthostatic hypotension and vasodilation. Opioid use might also cause syncope when used in doses meant to produce analgesia.

Methadone and buprenorphine are heart rate intervals even though most other opioids do not affect cardiac contractility (Mason et al., 2014).

Central nervous system effects: Long-term use of opioids in pain management is often associated with neurotoxicity which is of very high clinical significance especially in elderly patients. Other side effects that touch on the central nervous system are dizziness and loss of concentration and alertness. Hyperalgesia (thoroughly explained in section 2, subsection c) has also been reported as a central nervous system side effect in patients on chronic opioid therapy (Silverman, 2009). Studies have also proven depression to be of high prevalence among such patients, with comorbidity rates standing as high as 38% (Sullivan et al., 2010).

Musculoskeletal system effects: Long-term use of opioids in the management of pain is widely known to be associated with severe fractures and the increased risk of fractures, especially in the elderly (Miller et al., 2011). Research has given us no clear explanation as to why this is true. The current working theory, though, is that the opioids' effects on the central nervous system that produce dizziness and a decreased sense of alertness (especially true for morphine) play a role in this phenomenon (Vestergaard et al., 2006).

Effects on the endocrine system: In the long term, opioids have been shown to cause alteration in the release of all the hormones from the anterior pituitary gland (prolactin, adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, and lutein-stimulating hormone.) (Vuong et al., 2010). The production of sex hormones is also affected when opioids are used in long-term pain management as the gonadotropin-releasing hormone is suppressed resulting in their reduced production. This may eventually lead to hypogonadism (Ali et al., 2016).

Effects on the immune system and opioid-induced immunosuppression: Animal, cell culture studies, and in vitro experimental studies have revealed that use particular opioids with examples of morphine, fentanyl and methadone can cause interference of immune processes and increase the risk of susceptibility to diseases (Wiese et al., 2019) (Brack et al., 2011). Documentation has also been produced of an increased prevalence of pneumonia in elderly patients on chronic opioid therapy (Baldini et al., 2012). The exact way in which opioids interrupt immune processes and the pathophysiology of this effect is not yet clear, but research is ongoing. Therefore, long-term opioid use in the management of pain can eventually be shown to lead to opioid-induced immunosuppression.

Recommendations: As the long-term use of opioids in the management of pain has been shown to have many effects, the following recommendations might aid in the relief of some of these effects or their complete avoidance.

a. There is the need for mass teaching to aid people in the communities all around the world to gain knowledge of and develop a positive attitude toward addressing opioid overdose and addiction.

b. Abuse-deterrent opioids should be developed, utilized, and reviewed to curb the misuse and abuse of opioid agonists.

c. Proper evaluation and assessment of the health benefits versus the perceived future risks of the long-term utilization of opioids in the management of pain should be strictly adhered to when making the clinical decision to prescribe opioids to patients.

CONCLUSION

Opioids are very important in the analgesic sector of the medical field in the alleviation or annihilation of pain for patients with varying conditions. However, this does not mean that they are a panacea. All the limitations and effects of opioid use in the long-term management must be carefully considered when trying to maintain the equilibrium between them, their benefits, and the expectations of patients. Governments all around the world should work together with all health organizations to curb and curtail the ongoing opioid crisis concerning the abuse of these drugs.

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