

Review

Common Conditions Associated with Long Term Opioid Usage

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Abstract

Opioids are drugs that are used to manage wide range of chronic painful diseases. They are classified as broad-spectrum analgesics. They are frequently prescribed to manage cancer and chronic pain, post-operative pain among certain other conditions. However, there is a well-known phenomenon of psychological addiction that can develop with the use of opioids leading to prolonged use, abuse and misuse which undermines their clinical efficacy associated with their use. Although in some conditions long-term opioid therapy is needed. According to clinical recommendations, long-term opioid therapy involves taking opioids every day for more than three months. The criteria for defining long-term opioid therapy in clinical settings and research, however, vary. Certain conditions are associated with its long-term use including impaired cognitive effects, sedation, constipation, nausea, vomiting, physical dependence, tolerance, and respiratory depression which are quite common with the opioid treatment. Clinical concerns regarding addiction may hinder appropriate prescribing, resulting in insufficient pain management. Delay in stomach emptying, hyperalgesia, immunologic and hormonal abnormalities, muscular rigidity, and myoclonus are examples of less prevalent effects reported with long-term opioid use. Opioid induced constipation is commonly reported in long-term use and may get severe enough to necessitate stopping the opioids and cause underdosing and insufficient analgesia. Respiratory and sleep disorders also frequently observed in long-term users of opioids. Also, incidence of new episode of depression is quite commonly linked to the chronic use of opioid. The purpose of this research is to review the available information about common conditions associated with long term opioid usage.

Keywords: *opioid, pain, long-term, use*

Introduction

Natural and artificial substances that bind to one of the three major opioid receptor systems mu, kappa, or delta are referred as opioids. Opioids are categorized into natural and synthetic opioids. Addiction, misuse and overuse of opioids is very common. They have analgesic and central nervous system depressive effects, as well as the ability to generate euphoria. Opioids are powerful painkillers and have been explicitly authorized for analgesia for nearly 70 years. Even though overdose and opiate poisoning instances are frequently reported worldwide, opioids have generally been considered to be safe. The World Health Organization has identified opioid usage as a global health concern, and an opioid epidemic has been raging since the 1990s. Addiction to opioids is very high leading to dependence and long-term use (1). Opioids produce adverse effects in numerous organ systems via a number of ways. Evidence demonstrates that long-term opioid medication is linked to overdose, hypothalamic-pituitary-adrenal dysregulation, fractures, constipation, and sleep-disordered breathing. However, there are still a lot of knowledge gaps about the range of possible opioid-related negative effects. Opioid-related side effects have the potential to significantly lower quality of life and raise medical expenses (2).

As per clinical guidelines, long-term opioid therapy is the use of opioids on a daily basis for more than three months. However, there are differences in the standards used to define long-term opioid therapy in clinical settings and research (3). Long-term opioid use's negative impacts are a serious public health concern. Significant health hazards, including as lethal overdose and opioid use disorders, have been linked to long-term opioid usage in numerous studies. Long-term opioid therapy's alleged advantages have come under scrutiny. It has been suggested that the patients who are most likely to use opioids long-term are also those who are most at risk for worse outcomes related to pain, opioid addiction or dependency, or other unfavourable physical and mental health consequences. As per the adverse selection hypothesis, higher pain levels, more activity interference, more depression, and traits linked to opioid use disorders are patient risk factors for sustaining or prolonged opioid use, which lead to higher-risk opioid use such as high doses, use of more potent opioids, and concurrent use of alcohol or benzodiazepines (4).

Sedation, dizziness, nausea and vomiting, constipation, physical dependence, desensitization, and respiratory depression are common adverse effects of opioid

medications. Clinical concerns about physical dependence and addiction may hinder appropriate prescribing, which would result in insufficient pain management. Delay in stomach emptying, hyperalgesia, immunologic and hormonal abnormalities, muscular rigidity, and myoclonus are examples of less prevalent adverse effects. Constipation and nausea are the side effects of opiate use that are most frequently reported. Constipation in particular might be difficult to manage because there is often no tolerance to these adverse effects. They may be severe enough to necessitate stopping the opioids and cause underdosing and insufficient analgesia (5). The purpose of this research is to review the available information about common conditions associated with long term opioid usage.

Methodology

This study is based on a comprehensive literature search conducted on November 2, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about common conditions associated with long term opioid usage. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Constipation, tolerance, endocrinopathies, sleep disorders, cognitive impacts, respiratory depression, overdose, and addiction are among the opioid therapy's known side effects. Studies have revealed that greater daily opioid dosages, especially above a morphine equivalent oral daily intake of 100 mg, are associated with an increased risk of overdose and mortality. Since each pill contains a larger dose of medication, extended-release and long-acting opioid formulations may be advantageous for the complying patient but may also expose a higher risk for misuse if used improperly. In addition to the well-known negative effects of long-term opioid medication, it has just lately come to light that opioids can have substantial negative effects on sleep and central sleep apnea. Effectiveness and safety profile of chronic opioid therapy must be established through prospective, well monitored clinical trials (6).

Some of the common conditions associated with the long-term use of opioids are discussed below.

Opioid-induced constipation (OIC)

OIC is a common problem for chronic pain patients who depend on long-term opioid therapy. It is a challenging illness to manage and has a substantial psychosocial impact on people who experience it. Contrary to other opioid side effects, functional constipation does not go away with time after chronic opioid usage, and therapies for functional constipation frequently fail to relieve symptoms to a sufficient degree. The prevalence of OIC is estimated to vary. Reduced peristaltic and secretory actions are a direct result of opioid-induced bowel dysfunction, which is specifically brought on by mu-opioid receptors. As per the statistics, OIC affects 15% to 90% of opiate users (7) (8). OIC if not treated timely can lead to fatal outcomes as reported in a case by Kaushal et al. who described the presence of pneumoperitoneum on radiographic examination and collaboration with experts resulted in the diagnosis of stercoral colitis with potential micro-perforations due to long-term opioid usage. The patient first got better because of the fecal disimpaction and counselling, but eventually died (9).

The reported frequency of OIC from distinct trials was as high as 71%. OIC has been linked to major clinical and financial difficulties and may have a detrimental effect on patients' quality of life. Additionally, ongoing constipation can result in major medical complications such as intestinal obstruction and fecal impaction, which can increase the need for medical care and limit productivity (10). Results of a cross-sectional survey revealed that a low health-related quality of life for patients with chronic pain that requires long-term opioid treatment, leading to constipation and the use of laxatives, as well as a high degree of moderate to very severe abdominal symptoms, a high degree of self-management of OIC, and a low degree of satisfaction with laxatives. Patients with OIC who have poor quality of life and persistent symptoms despite taking two or more laxatives are a vulnerable patient population who require optimal healthcare management and may also gain from more specialized and cutting-edge treatments (11).

Respiratory depression and sleep disorders

The primary cause of opioid-induced death is opioid-induced respiratory depression, which is the neurological suppression of respiratory drive that results in ventilatory insufficiency along with a lowered level of consciousness and obstructive sleep apnea. The risk is increased by individual variances in physiological and

neurological conditions such as anesthesia, sleep-disordered breathing, and concurrent drug administration as well as variability in responses to opioids. It is unknown which locations are required for the induction of opioid-induced respiratory depression because several different sites can independently have a depressing effect on breathing. The preBötzing complex in the ventrolateral medulla is the source of inspiratory rhythm (12). Patients who use opioids chronically as for more than six months are more likely to develop Biot's respiration, ataxic breathing, or both, which is an erratic breathing pattern accompanied by central apneas during sleep. It differs from Cheyne-Stokes respiration or periodic breathing with central apneas. Other individuals seen at this elevation who have been referred for a sleep apnea screening but have not been using opioids hardly ever exhibit these ventilatory patterns. It may not be true and the shift in hypoxic ventilatory regulation with sleep may help to explain this that continuous opioid administration is safe because users become tolerant to their respiratory-depressing effects. The impact of regular sleep on respiratory regulation patterns, including changes in susceptibility to hypercarbia, hypoxia, and respiratory rhythmicity, has long been known (13).

Opioids are linked to a number of sleep-related breathing disorders, including central sleep apnea, hypoxemia, and other types of aberrant breathing patterns. However, a considerable number of individuals taking chronic opioids may experience undiagnosed central and obstructive sleep breathing problems, which could lead to an increase in morbidity and mortality (14). Since opioid peptides are thought to be involved in the induction and maintenance of the sleep state and opioid receptors are found in the same nuclei that are involved in sleep regulation. The most widely used opioids are mu-opioids, which are known respiratory depressants that lead to aberrant awake ventilatory responses to hypoxia and hypercapnia (15). Results of a cross-sectional study showed that all chronic opioid medications used by the study population were shown to be more closely related to sleeping issues than the detoxification group. Patients who had just quit using drugs undergoing opioid detoxification had noticeably fewer sleep disruptions than those who continued using opioids (16).

Long-term opioid abuse has a deleterious impact on sleep on two levels: breathing during sleep and sleep architecture complications of which can affect the daily life of patients. Poor sleep, irregular breathing during

sleep, and daytime performance may be correlated (17). Chronic opioid usage has been demonstrated to interfere with appropriate sleep/wake behaviour, which frequently shows up as daytime sleepiness and insomnia. Chronic opioid use's impact on sleep is a major contributor to drug misuse, relapse, and depression. Patients with chronic pain are more vulnerable to the harmful effects of opioid-induced sleep issues because sleep deprivation can make pain symptoms worse. Despite the abundance of studies describing the detrimental effects of opioid medications on sleep, it is still unclear how opioids disturb sleep (18).

Cognitive effects and sedation

One of the main causes of opioid usage cessation is cognitive effects and sedation, which are common in individuals with chronic non-malignant pain undergoing long-term opioid medication. The phenomenology of cognitive effects and sedation includes somnolence, sleep disturbances, lethargy, inability to focus, memory abnormalities, psychomotor dysfunction, visual distortions, and executive dysfunction. Deficits may result from a combination of these and other causes, from unrelieved pain, opioid therapy, or both. Mechanisms include those that affect the central nervous system, such as those that have a direct toxic effect on neurons and cause a reduction in consciousness, those that have a direct impact on processing and reaction and cause cognitive or psychomotor impairment, and those that have inhibitory effects on cholinergic activity. Memory problems in 73%–81% cases, sleep disturbances in 35%–57% cases, and fatigue in 10% of cases are the three most common cognitive effects and sedation. Extreme cognitive dysfunction can cause delirium and diminished awareness which can lead to coma when it is at its worst. In particular for the elderly, emotional anguish, sleep issues, and other comorbidities and therapies might make cognitive effects and sedation worse (19).

Although there is a dearth of empirical research on the neurocognitive effects of acute and chronic opioid use, what is known so far suggests that opiate use affects cognitive function both immediately and over time. Neuropsychological research links both acute and chronic opioid use to impairments in attention, focus, memory, visuospatial skills, and psychomotor speed. The ability to change cognitive focus and restrain incorrect reaction inclinations appear to be most affected by the long-term side effects of opiate use (20). Although the exact sequence of events is unknown, chronic opioid use is a risk factor for delirium, which is linked to a

higher risk of dementia. Opioids sedate people, which has a reversible effect on cognition. Furthermore, autopsy studies have revealed neuropathologic characteristics in young opioid users that are comparable to those found in Alzheimer's patients. Opioids alter the function of microglia, immune cells that control inflammation in the brain and may play a role in neurodegenerative illnesses like Alzheimer's disease. Finally, opioids encourage microglial and neuronal death. All of this data points to a potential link between chronic opioid usage and cognitive deterioration (21).

Depression

Over the past two years, it has been seen that opioid therapy not only raises the risk of new onset depression independently but is also predicted by depression. The possibility that long-term opioid use results in depression complicates pain management in unexpected ways. Long-term opioid use is associated with a 35%-100% increased risk of new-onset depression, but not higher doses, and opioid exposure is related to a 100% increased risk of depression recurrence. Long-term opioid therapy complicates rather than makes treatment of concurrent depression easier, which portends a probable rise in what may have been an otherwise avoidable depression. These opioids may elevate mood temporarily when used to treat chronic pain, but they are likely to make depression worse over time (22). Salas et al. revealed in their study findings that in those without a history of chronic opioid analgesic use, 31–90 days were linked to new depressive episodes but not insomnia. The effects of prolonged >90 days opioid analgesic use were shown to be more pronounced in persons with insomnia than in those without. All stratum-specific effects, though, did not differ significantly from one another. There was evidence for a tendency that chronic opioid analgesic usage is a greater risk factor for new depressive episode in individuals with insomnia than in those without, even if stratum-specific risks were statistically identical (23).

Merril et al. demonstrated in their study findings that patients on long-term opioid therapy reported increased levels of psychosocial issues and patients receiving higher doses were also more likely to exhibit clinical depression (24). Longer duration of usage, but not dose, is linked to opioid-related new onset of depression. Patients and healthcare professionals alike should be aware of the risk of new-onset depression associated with opioid analgesic use longer than 30 days. A corresponding but undetected rise in depression may be seen by the sizable patient group getting opioid medication. Incentives for public health and pain

treatment can be influenced by conclusively proving that higher doses, longer durations, or both of opioid analgesic usage are linked to the onset of depression for the first time in a variety of patient populations (25). Present literature advocates for utmost need of further clinical research including population-based epidemiological studies to evaluate the conditions and effects associated with long-term opioid use since the available studies are quite limited and to develop safe guidelines for use long-term opioid therapy where needed.

Conclusion

Long-term opioid therapy is often needed in management and treatment of cancer pain and chronic pain among certain other conditions however, the risk of various conditions and comorbidities associated with the long-term use shall not be neglected. Additionally, in order to maximize the effectiveness of opioid therapy while minimizing the severity of side effects and adverse events, patients should be properly screened, educated, and treated for any potential side effects in advance.

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Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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