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General

Methadone for Chronic Pain: A Review of Pharmacology, Efficacy, and Safety Concerns

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Purpose of Review

Methadone is a synthetic opioid extensively used in opioid use disorder management but is gaining recognition for its unique pharmacological properties that make it a viable alternative for chronic pain management. This review aims to explore methadone's pharmacokinetics, pharmacodynamics, efficacy, and safety profile to assess its potential role in managing chronic pain conditions.

Recent Findings

Methadone's dual action as a mu-opioid receptor agonist and NMDA receptor antagonist positions it as an effective option for managing both nociceptive and neuropathic pain. It has shown promising results in cancer pain management, refractory pain, and opioid rotation strategies. Despite its therapeutic advantages, concerns regarding its narrow therapeutic window, variable pharmacokinetics, QT interval prolongation, and risk of respiratory depression highlight the need for careful patient selection and monitoring. New evidence also sheds light on its affordability and efficacy in low-resource settings, as well as its controversial role in mitigating opioid-induced hyperalgesia.

Summary

Methadone offers a unique therapeutic option in chronic pain management due to its multifaceted pharmacological properties. While it provides significant benefits for patients with complex pain syndromes, clinicians must exercise caution due to its safety concerns and variability in individual metabolism. A personalized approach, combined with rigorous monitoring, is essential to optimize its benefits while minimizing risks. Further research is needed to better define its role in chronic pain treatment and address unresolved safety concerns.

INTRODUCTION

Chronic pain affects over 25% of adults in the United States, making it one of the most prevalent issues in outpatient medical care.[1] Among this population, approximately 20 million people endure severe, debilitating chronic pain, underscoring the critical need for healthcare providers to develop effective management strategies.[1] Chronic pain, defined as pain persisting for more than three months, has profound implications for patients' quality of life due to its pervasive nature.[1,2]

Effective management of chronic pain often necessitates a multidisciplinary approach that combines pharmacological treatments with nonpharmacological interventions.[2,3] Initial pharmacotherapy options typically involves acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), while opioids are reserved for cases of severe, persistent pain unresponsive to other therapies or when pain significantly impacts quality of life.[3] However, the opioid epidemic has shifted attention toward alternative pain management strategies, bringing methadone into focus for its unique analgesic properties and cost-effectiveness, particularly in low-resource settings.[4,5] In this context, methadone has gained attention for its unique analgesic properties and potential role in chronic pain management.[6]

Methadone, a long-acting synthetic opioid, was first discovered by German scientists during World War II as a response to a morphine shortage, and was later introduced into the United States in 1947 as an analgesic.[4,6,7] Now classified as a Schedule II drug under the Controlled Substances Act, methadone is widely recognized for its role in treating opioid addiction.[7] Despite limited literature on

its effectiveness in pain management settings, methadone holds promise as a cost-effective alternative to long-acting opioids. Its affordability may help improve access to pain management, particularly in low-income populations and developing countries.[4,6]

Methadone has unique characteristics that have made it appealing as an analgesic in chronic pain. In addition to being a highly potent mu-opioid agonist, it prevents monoamine reuptake in the central nervous system and inhibits presynaptic N-methyl-d-aspartate (NMDA) receptors. These properties allow for pain mitigation and recovery promotion while reducing the development of hyperalgesia and opioid tolerance.[6] Methadone has also been found to produce stable plasma concentrations after a single dose, in contrast to its short-acting opioid counterparts, and has a reported elimination half-life of 24 to 36 hours, preventing patients from experiencing breakthrough pain after administration.[8] Although methadone presents many favorable characteristics, it has been found to have a wide interindividual variability in pharmacokinetics, highlighting the need for healthcare providers to increase their awareness and understanding of this medication prior to dispensing.[6]

This review article aims to provide an overview on methadone's pharmacokinetics, pharmacodynamics, potential side effects, safety profile, and its efficacy in the treatment of chronic pain conditions.

PHARMACOKINETICS AND PHARMACODYNAMICS OF METHADONE

Methadone is a synthetic opioid composed of L-methadone, the active isomer, and D-methadone.[9] It produces analgesia and euphoria by activating mu opioid receptors in the central nervous system and gastrointestinal tract through Gi-protein signaling.[10] Additionally, it reduces opioid tolerance by promoting receptor internalization and recycling.[11]

Methadone is also a noncompetitive antagonist at NMDA receptors and inhibits serotonin reuptake through inhibition of the serotonin transporter (SERT) and binding to 5-HT2A receptors, making it efficacious for neuropathic pain.[11] Evidence in the literature suggests methadone's antagonism of NMDA receptors modulates neuropathic pain and prevents remodeling of pain pathways that result in pain chronification.[2] In addition, methadone inhibits the noradrenaline transporter (NET) further contributing to its analgesic effects.[12]

Oral methadone is fat soluble and rapidly absorbed after administration. It goes through a first pass effect and then is detectable in the plasma after thirty minutes.[9] Oral bioavailability is about 60-70% but varies widely amongst patients.[13] There is a large variance in time to peak concentration ranging from one to five hours. For chronic users this can be due to the drugs induced slowing of gastric emptying. Overall, desired effect of methadone can begin within thirty to sixty minutes and continue for four to six hours.

Methadone has a half-life of approximately twenty-five hours. This long retention is potentially due to its extensive binding to plasma proteins.[13] It specifically binds to alpha1-acid glycoprotein which has implications for patients in disease states as they may have a higher concentration of alpha1-acid glycoprotein therefore altering the concentration of free methadone. Concentration can be affected by many drugs that may cause displacement of methadone from plasma proteins like propranolol, phenothiazines, and imipramine. Other medications like tricyclic antidepressants, progesterone, and lidocaine may selectively compete for protein binding sites causing free levels to potentially increase as well.[13]

Methadone is metabolized into inactive molecules by cytochrome P450 enzymes in the liver and gut primarily through the N-demethylation by CYP3A4 to the inactive metabolite 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP).[9] There is a varying spectrum of activity of the CYP3A4 amongst individuals resulting in large differences in methadone bioavailability person to person. Furthermore, medications such as antiretrovirals that induce CYP3A4 can reduce methadone levels, potentially leading to withdrawal symptoms.[14]

EFFICACY OF METHADONE IN CHRONIC PAIN MANAGEMENT

METHADONE FOR REFRACTORY AND CANCER PAIN

Methadone has been widely used in the management of cancer pain, particularly in patients who have not responded to other opioids. Its unique pharmacological profile makes it a valuable option in palliative care. Methadone acts as a potent mu opioid receptor agonist and NMDA receptor antagonist, which contributes to its efficacy in managing complex and severe pain states often seen in cancer patients.[15] Studies have shown that methadone can provide effective pain relief and improve the quality of life in cancer patients, making it a critical component in oncological pain management protocols. In a review of ten different articles with methadone as a first-line therapy for cancer pain, it was found to be as effective as other opioids including Fentanyl with its analgesic and antihyperalgesic properties.[16] It also had similar adverse effect profiles when compared to similar opioids, which is important to recognize given that one concern for methadone is the potential for accumulation and delayed toxicity.[15]

Methadone can target multiple pain pathways, allowing for a more comprehensive approach to pain relief. In a 2022 study by Ding et al., 90 patients with refractory pain despite multiple prior opioid medication treatments were offered methadone as an alternative.[17] 71% (64/90) of patients had a statistically significant drop in their pain score and daily frequency of breakthrough pain. Importantly, this also decreased the daily cost of analgesic treatment for these patients, as methadone is dramatically cheaper than alternative opioids.[17] Methadone is one of the most affordable chronic pain medications, costing around $15–$30 for a 30-day supply, while other options like tramadol and morphine range from $20–$200, oxycodone from $150–$300, and fentanyl patches from $50–$200.[18] Of course, prices vary by location, insurance coverage, and formulation,

making methadone a cost-effective choice for many patients.

METHADONE FOR NEUROPATHIC PAIN

Neuropathic pain, resulting from damage to the nervous system, presents a significant challenge in pain management due to its resistance to conventional analgesics. Similar to its effects for cancer patients, methadone's dual mechanism of action renders it particularly effective for neuropathic pain. In a trial of 18 patients with neuropathic pain, specifically mechanical allodynia and radiculopathy, methadone was offered as a therapeutic option. Notably, 70% (9/13) of patients had complete resolution of their mechanical allodynia, and 100% (8/8) of patients had resolution of their shooting pain.[19] Further, in a 2005 review of 13 cases involving methadone for neuropathic pain, it was found that methadone was effective at relieving pain and improving quality of life and sleep in 62% of patients resistant to conventional analgesics.[20]

OPIOID-INDUCED HYPERALGESIA

Opioid-induced hyperalgesia (OIH) is a paradoxical phenomenon where prolonged opioid use leads to a reflexive increased sensitivity to pain. There is conflicting evidence that methadone's NMDA receptor antagonism may counteract this development of OIH, which could make it a good choice for long-term opioid therapy.[21] Some research indicates that switching patients from other opioids to methadone can result in a significant reduction in OIH symptoms and improved pain control. In a 2008 case report, a patient with small cell lung cancer and chronic OIH reported a significant decrease in pain intensity, from 8 to 3 on a visual analogue scale, after reducing their hydromorphone dose by 40-50% and beginning methadone treatment.[22] Furthermore, in a review of OIH in humans, Chu et al. identified six different published reports where methadone significantly improved or resolved suspected OIH.[23]

However, it must be noted that data has also been published suggesting methadone does not improve OIH, or may even worsen the pain symptoms. In a 2015 literature search, there was evidence to suggest that in former opioid addicts who were on methadone maintenance therapy, there was an increased risk for the development of OIH.[24]

Methadone may mitigate OIH through NMDA receptor antagonism, although evidence is mixed. Further research is needed to confirm its role in managing OIH.

LONG HALF-LIFE AND LESS FREQUENT DOSING

One of the notable pharmacokinetic properties of methadone is its long half-life. It is readily absorbed orally and through the lower gastrointestinal tract, and becomes detectable in the plasma within 30 minutes with peak levels at 2–4 hours. It also maintains sustained levels for over 24 hours.[25,26] This extended half-life allows for less frequent dosing compared to other opioids, potentially improving patient adherence and convenience. The steady plasma levels achieved with methadone reduce the likelihood of breakthrough pain and withdrawal symptoms, contributing to better overall pain management.[27] However, the variability in methadone's half-life necessitates careful dosing and monitoring to avoid accumulation and potential toxicity.[25]

SAFETY PROFILE AND ADVERSE EFFECTS

Methadone, just as with all opioids used for treating chronic pain, has a complex side effect profile that requires vigilant monitoring, particularly when used for chronic pain syndromes. In a systematic review of methadone published in 2021 that reviewed 40 randomized controlled trials, the most common side effects of this medication were nausea experienced in 60% of patients, vomiting (45%), and drowsiness (35%).[2] These side effects were no different than other analgesics trialed in the study, including morphine and fentanyl. Cognitive impairment and a reduced ability to perform daily activities also occurred.[28] Chronic methadone use can lead to physical dependence, and abrupt discontinuation may result in withdrawal symptoms. Methadone's metabolism via the CYP450 enzyme system, particularly CYP3A4, introduces the potential for significant drug interactions.[6] Medications such as benzodiazepines, certain antidepressants, and other opioids can increase sedation and respiratory depression, further complicating its use.[29]

One of the primary risks of methadone is respiratory depression, which can be life-threatening. Methadone's complex pharmacokinetics make proper titration challenging, and for this reason it can have the propensity to be overprescribed leading to complications. For instance, between 1999 and 2009, the rate of fatal methadone overdoses increased five-fold as methadone became a more popular treatment for chronic pain.[30] This led to the FDA releasing a public health advisory in 2006 to raise awareness of the unintentional overdoses from methadone.[31] The risk of respiratory depression is particularly high when the patient is first introduced to the medication, because the half-life is profoundly longer than most typical pain medications.[32] Due to current concerns for respiratory depression, it is now advised that all patients starting on methadone should be clinically reassessed in three to five days following initiation to evaluate side effects.

Another critical safety concern is methadone's potential to prolong the QT interval on an electrocardiogram (ECG). QT prolongation can increase the risk of torsade's de pointes, a potentially fatal ventricular arrhythmia.[6,32] Risk factors such as high methadone doses, concurrent use of other QT-prolonging drugs, or pre-existing cardiac conditions heighten this concern. For this reason, baseline and periodic ECG monitoring are often recommended for patients on methadone therapy, particularly at higher doses or when other risk factors are present.[33]

Methadone should only be initiated by physicians with experience in pain management due to its complex pharmacological profile and risk factors. It is not recommended for use in opioid-naive patients, as they are at an even

Benefits and Risks of Methadone

Benefits	Risks
Effective for both nociceptive and neuropathic pain due to dual mechanisms (mu-opioid agonism and NMDA antagonism)	Risk of respiratory depression, particularly during initiation
Prolonged half-life allows for less frequent dosing and stable plasma levels, reducing breakthrough pain	QT interval prolongation, increasing risk of torsade de pointes
Potentially mitigates opioid-induced hyperalgesia (OIH)	Complex pharmacokinetics with significant interindividual variability
Cost-effective option compared to other long-acting opioids	Drug interactions with CYP450 enzyme inhibitors and inducers
	High risk of overdose and death if misused or self-escalated

higher risk for severe adverse outcomes. Patients must be extensively counseled against self-escalating their methadone dose under any circumstances, as this significantly increases the risk of overdose and death. Close supervision and patient education are critical to ensuring safe and effective use of methadone in pain management.

A summary of the benefits and risks of methadone are presented in the table.

METHADONE IN OPIOID DEPENDENCY

Methadone is not only a valuable medication for chronic pain but also plays a critical role in the treatment of opioid dependency. As a full mu-opioid receptor agonist with a long half-life, methadone reduces withdrawal symptoms and cravings in individuals with opioid use disorder (OUD), allowing for stabilization and gradual recovery.[34-36] It has been widely used in medication-assisted treatment (MAT) programs and remains a cornerstone therapy for opioid dependency due to its ability to diminish the highs and lows associated with shorter-acting opioids.[36] Additionally, methadone is often compared to buprenorphine, another key MAT option, which acts as a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist.[37-39] Buprenorphine has a ceiling effect on respiratory depression, making it potentially safer in certain populations, but it may not be as effective as methadone for individuals with higher levels of physical dependency.[38] Both medications, however, have demonstrated significant success in reducing opioid-related morbidity and mortality and should be considered based on individual patient needs and treatment goals. Methadone's dual utility in pain management and addiction treatment underscores its importance in addressing the overlapping public health crises of chronic pain and opioid dependency.

CONCLUSION

Methadone offers a distinct and valuable option for managing chronic pain, particularly in cases where conventional opioids prove inadequate. Its unique pharmacological properties, such as NMDA receptor antagonism and an extended half-life, enable it to effectively treat both nociceptive and neuropathic pain while potentially reducing OIH. However, its narrow therapeutic index, individual variability in metabolism, and risk of QT interval prolongation necessitate careful patient selection, close monitoring, and thorough patient education.

Clinicians must adopt a personalized and cautious approach when prescribing methadone, taking into account its drug interactions and potential for significant adverse effects. By adhering to established safety protocols and actively engaging patients in their care, healthcare providers can leverage methadone's benefits while minimizing risks, ultimately enhancing the quality of life for individuals with chronic or cancer-related pain.

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