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Developing Non-Opioid Therapeutics to Alleviate Pain Among Persons with Opioid Use Disorder: A Review of the Human Evidence

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Abstract

The opioid crisis remains a major public health concern, causing significant morbidity and mortality worldwide. Pain is frequently observed among individuals with opioid use disorder (OUD), and the current opioid agonist therapies (OAT) have limited efficacy in addressing the pain needs of this population. We reviewed the most promising non-opioid analgesic therapies for opioid-dependent individuals synthesizing data from randomized controlled trials in the Medline database from December 2022 to March 2023. Ketamine, gabapentin, serotoninergic antidepressants, and GABAergic drugs were found to be the most extensively studied non-opioid analgesics with positive results. Additionally, we explored the potential of cannabinoids, glial activation inhibitors, psychedelics, cholecystokinin antagonists, alpha-2 adrenergic agonists, and cholinergic drugs. Methodological improvements are required to advance the development of novel analgesic strategies and establish their safety profile for opioid-dependent populations. We highlight the need for greater integration of experimental pain methods and abuse liability assessments, more granular assessments of prior opioid exposure, greater uniformity of pain types within study samples, and a particular focus on individuals with OUD receiving OAT. Finally, future research should investigate pharmacokinetic interactions between OAT and various non-opioid analgesics and perform reverse translation basic experiments, particularly with methadone and buprenorphine, which remain the standard OUD treatment.

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7.Disclosure statement

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Keywords

Non-opioid Analgesics; Pain Sensitivity; Opioid Use Disorder; Experimental Pain; Pharmacotherapy Development

1. Introduction

The opioid crisis has created a harrowing legacy of overdoses, disability, and disenfranchisement (1). Some projections estimate nearly half a million fatal opioid overdoses in the US over this decade alone (2). Far from being a North American exclusivity, this urgent problem has advanced in China, Europe, Australia, and Iran, as well as in Africa and in other parts of the developing world (1, 3–5).

Pain is a significant contributor to the opioid crisis, with as many as 60% of persons who develop opioid use disorder (OUD) reporting pain as the main reason for their first opioid use (6). Up to 10% of persons with chronic pain eventually develop OUD, and up to 55% of those with OUD also continue to experience chronic pain (7, 8). While opioids effectively treat acute pain, their usefulness for chronic pain management remains debatable (9). In fact, patients receiving long-term opioid therapy (LTOT) may continue to experience pain despite receiving extremely high doses of opioids (10). Various factors can limit the therapeutic utility of opioids, including disease progression, tolerance, and hyperalgesia (11). Opioid-induced hyperalgesia (OIH) is characterized by exacerbated pain intensity over time, including the spreading of pain sensation to other body sites, and an increased pain sensation to external stimuli (12, 13). Moreover, OIH may require a tapering of the opioid dose or a change to another opioid agonist. On the other hand, opioid tolerance is characterized by a reduction of opioid efficacy, leading to the requirement of higher doses to produce the initial level of analgesia, which is generally accompanied by more adverse effects. Growing evidence from neuroimaging studies shows that chronic pain and OUD feature states of compromised dopamine mesocorticolimbic transmission, which impair one’s ability to experience positive feelings from environmental stimuli (14, 15). Further, pain relief is inherently rewarding, an effect that is dependent on cortical opioid signaling and dopaminergic activation of the midbrain and nucleus accumbens (14). Thus, similar mechanisms underlie pain relief and the reinforcement and maintenance of addictive behavior (Figure 1) (14). As pain becomes chronic, the brain pathways that control pain and motivation are dysregulated, leading to heightened pain sensitivity and anhedonia, thereby worsening the individual’s quality of life (16). Consequently, the individual is then progressively driven to seek satisfaction not from natural rewards, but from opioid-derived pharmacological stimulation.

A systematic review of experimental pain studies showed that patients with OUD on opioid agonist therapy (OAT) have had doses of opioid analgesics titrated to as much as 20 times the doses used for severe pain in opioid naïve patients without obtaining similar pain relief (10). Despite becoming highly tolerant to opioid-induced analgesia, OUD patients on OAT are still vulnerable to opioid-induced respiratory depression and abuse potential, narrowing the therapeutic window of opioid analgesics in this population (10). Taken together,

these clinical phenomena add to the high morbidity and mortality of persons with OUD. Considering that pain is a multifaceted experience mediated by multiple neurotransmitter systems (Figure 1), novel, non-opioid therapeutic strategies that circumvent these challenges are urgently needed (17, 18).

To address this need, we reviewed studies investigating non-opioid pharmacotherapies for pain among individuals with opioid dependence, which includes persons with OUD and persons receiving LTOT. After synthesizing the data from existing clinical trials, we offer methodological, mechanistic, and clinical insights to guide future pain and addiction research and treatment.

2. Methods

We searched MEDLINE without language or date restrictions between December 2022 and March 2023. Our search strategy used the terms analgesia, pain, pain scores, laboratory pain, experimentally evoked pain, opioid use disorder, opioid dependence, opioid addiction, long-term opioid therapy, refractory or intractable pain, and terms related to each of the following described non-opioid medications. The full search strategy is reported in the supplementary material (Appendix 1). Reference lists from identified studies and review articles were examined to find additional studies that were not identified by the main search.

Eligible reports for our review included studies that involved: (1) individuals with OUD or those receiving LTOT for pain (i.e., with a cumulative opioid use duration of more than three months) (19); (2) pain measures as reported outcomes (clinical or experimentally induced pain); (3) prospective, interventional clinical trial designs; and (4) administration of at least one of the following non-opioid medications: alpha-2-adrenoreceptor agonists, antidepressants (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants), cannabinoids, cholecystokinin antagonists, cholinergic agents, gabapentinoids, gamma-aminobutyric (GABA) agonists, glial activation inhibitors, N-methyl-D-aspartate (NMDA) antagonists (ketamine or dextromethorphan), or serotoninergic psychedelics. Conversely, studies were excluded from our review if they: (1) were not original research; (2) had not undergone a peer-review process; or (3) included participants with opioid use of less than three months or with an unspecified duration of use, to guarantee the study samples consisted of opioid-dependent individuals.

The tables summarize the randomized controlled trials examining non-opioid medications in opioid-dependent patients with chronic non-cancer pain. Although cancer pain studies were not displayed in the tables as they fell outside the scope of the review, relevant data are briefly discussed in the respective drug class sections. These studies proved informative in illustrating the potential of non-opioid medications to alleviate pain in patients who use opioids, but given the distinct nature of pain mechanisms associated with cancer pain their significance in the review was secondary. Furthermore, we provided a general overview of pertinent literature that did not satisfy all eligibility criteria but nonetheless provided valuable clinical or mechanistic insights.

3. Results

We identified 14 randomized controlled trials that provided relevant data addressing our research question. These studies are summarized in tables and described throughout the text. Among these trials, six were laboratory pain studies and eight were clinical trials. Twelve studies primarily focused on patients with OUD, while only one included patients receiving LTOT. Within the studies that met our eligibility criteria, three human laboratory studies examined the effects of glial activation inhibitors on pain relief; one study utilized CCK antagonists as an adjuvant to opioids; two studies investigated the analgesic effects of gabapentinoids; one clinical trial explored the use of GABA agonists as an adjuvant treatment to morphine, and one study employed alpha-2 adrenergic agonists for intra-operative pain management. Four other studies investigated the effects of NMDA antagonists on pain relief (one using dextromethorphan and three using ketamine). Additionally, one clinical trial examined cannabinoids as an adjuvant treatment for chronic pain patients on LTOT, and one study explored the use of antidepressant medications in OUD patients. Furthermore, five studies also described opioid consumption as a primary outcome, while the typical adverse effects of opioid agonists, such as abuse potential and respiratory depression, were inconsistently reported.

3.1 Gabapentinoids

Gabapentin is a GABA-analog anticonvulsant commonly used to manage chronic neuropathic pain syndromes. Its analgesic mechanism of action is still poorly understood but appears to be related to a diminished expression of neuronal voltage-gated calcium channels, leading to a cellular hyperpolarization (20). Notably, neuropathic pain and OIH share common pathophysiological pathways involving a heightened sensitivity of the central nervous systems (CNS) to nociceptive stimuli and autoimmunity, which are speculated to benefit from the anti-excitatory and anti-inflammatory effects of gabapentin (21).

A seminal study by Compton et al. showed that a daily dose of 2400 mg of oral gabapentin significantly attenuated OIH in individuals receiving methadone therapy, as demonstrated by increased pain threshold and tolerance compared to controls in an experimental pain model (22). A recent crossover trial recruited patients on OAT with either methadone or buprenorphine/naloxone and evaluated their acute experimental pain responses under the following interventions: increasing their maintenance opioid dose by 30%; adding a single 600 mg dose of gabapentin; adding oxycodone; adding placebo. There were no significant differences between groups on the primary outcomes of pain threshold and tolerance, measured using the cold pressor test, in either arm of the study. However, in the methadone arm, those who received gabapentin or an extra 30% of methadone reported significantly lower pain intensity and, in the case of the gabapentin group, greater satisfaction with the treatment (see Table 1. Gabapentinoids) (23).

Despite not investigating pain specifically, trials with larger samples and longer treatment duration have found that add-on gabapentin therapy led to decreased opioid consumption in opioid-dependent patients on OAT (24). This may be related to gabapentin’s ability to mitigate pain during opioid withdrawal (24). In contrast with these findings, a systematic

review and meta-analysis of 281 trials found no clinically significant analgesic or opioid-sparing effects of perioperative gabapentinoids for postoperative pain management (25).

In terms of the combined treatment of opioids for cancer pain, a 2017 meta-analysis of randomized controlled trials reported no clinically significant advantage of gabapentinoids (26). However, a subsequent meta-analysis in 2021 indicated that the combination of gabapentin and opioids was more effective than opioids alone for treating neuropathic cancer pain (28).

Although seemingly advantageous for intractable neuropathic pain (27), and backed by a small body of evidence supporting its potential for the management of OIH, the combination of gabapentinoids with opioids needs to be approached with caution. Recent meta-analytic data points to increases in adverse events related to CNS depression and higher mortality with combined opioid and gabapentinoid therapy (28), though higher-quality evidence is still necessary to establish the risk/benefit ratio of this approach.

3.2 GABA Agonists

The analgesic properties of GABAergic drugs are likely connected to the widespread distribution of GABA receptors and GABAergic neurons along CNS pathways modulating pain perception, as well as the presence of GABA receptors in afferent nerve fibers that transmit painful stimuli (29). Changes in GABAergic neurotransmission are an essential step in mediating opioid analgesia (30), and brain levels of GABA have been considered as potential biomarkers of pain disorders (31). While animal models of pain have long attested to the antinociceptive properties of GABAergic drugs (29), their long-term risk/benefit ratio in humans remains controversial.

The GABAergic drug study that most closely addresses the topic of this review is a clinical trial of intramuscular midazolam plus haloperidol given with morphine to patients with OUD who presented to the emergency department with severe acute pain. In this study, cases experienced lower pain scores and a decreased need for additional morphine compared to controls (see Table 2. GABA Agonists) (32).

The literature investigating GABAergic drugs as analgesics for populations not diagnosed with OUD is much more robust. Epidural midazolam proved equivalent to epidural steroids for chronic low back pain in at least one clinical trial and has been used off-label for years (33, 34). Oral clobazam has also shown an analgesic effect for chronic low back pain patients but produced no verifiable benefit on experimental pain measures (i.e., quantitative sensory testing) (35). Clinical studies assessing the addition of midazolam to morphine intrathecally for post-operative analgesia have yielded improved pain control and less opioid usage (36). Similar effects have been achieved with epidural baclofen, a GABA-B agonist (37). One clinical trial tested the addition of midazolam to morphine-based epidural terminal cancer pain therapy, finding no benefit (38). However, this negative result may have been due to the low dose imposed by the study’s design.

Overall, there is a lack of experimental research on the efficacy of GABAergic drugs in pain management for opioid-dependent individuals. One of the main challenges in studying

GABAergic agents as analgesics is distinguishing the effects of their additional properties, such as hypnotics, sedatives, muscle relaxants, and anxiolytics, on patients' pain perception. To address this issue, incorporating experimental pain measurements into clinical studies and developing drugs with more selective mechanisms of action may provide insight into this research question. Furthermore, increasing pharmacological selectivity can help minimize the risky interactions between opioids and GABAergic drugs.

3.3 Alpha-2 Adrenergic Agonists

The adrenergic system is thoroughly involved in modulating pain signaling. In the spinal cord, alpha-2 adrenergic presynaptic receptors block norepinephrine release, which is modulated by descending inhibitory pathways (39). These tracts inhibit spinal pain transmission, promoting endogenous analgesia. As a result, alpha-2-adrenoceptor agonists have unique analgesic properties distinct from their other pharmacological effects, such as alleviating opioid withdrawal symptoms (40).

The most compelling evidence in favor of the analgesic effects of alpha-2 adrenergic agonists, such as dexmedetomidine and clonidine, comes from research among cancer patients that require LTOT (41). In contrast, only a limited number of studies have explored the impact of these drugs on chronic non-cancer pain, and even fewer studies evaluated patients with both pain and OUD (see Table 3. Alpha-2 Adrenergic Agonists). Most clinical trials applied neuraxial injection, such as intrathecal and epidural, to limit the undesirable side effects resulting from non-specific activation of adrenergic receptors (42, 43). Two retrospective studies confirm this method is helpful to alleviate pain in medical procedures, such as vaginal and cesarean delivery, among persons with OUD on methadone or buprenorphine (44, 45). However, the invasiveness of this procedure may limit its use in other clinical scenarios.

Regarding less invasive administration, evidence has been limited to observational studies and expert opinions. A few case reports describe pain improvement after intravenous dexmedetomidine in patients with vaso-occlusive episodes in patients with sickle cell disease who have failed to respond to or displayed detrimental adverse effects for escalating doses of opioids (46, 47).

Overall, there is a dearth of research exploring the potential of alpha-2 adrenergic agonists to relieve non-cancer pain in patients exposed to opioids for extended periods. A significant hurdle to studying these drugs as analgesics is their induction of systemic adverse effects including bradycardia and hypotension. Further investigation is needed to determine optimal dosing and safety parameters, as well as appropriate patient selection for alpha-adrenergic agonists.

3.4 Glial Activation Inhibitors

Mounting evidence suggest that the activation of glia, the immune cells of the CNS, can impact the mechanisms underlying opioid reward, tolerance, and withdrawal (48). These findings have paved the way for the clinical and translational exploration of glial activation inhibitors, including minocycline, ibudilast, propentofylline, and pannexin-1-

channel inhibitors, as potential non-opioid pharmacotherapies for the significant challenges associated with prolonged opioid use, such as opioid-induced hyperalgesia and withdrawal.

Overall, the existing human studies highlight the potential analgesic and opioid withdrawal-suppressing effects of glial activation inhibitors. Among the three prospective clinical trials administering glial activation inhibitors to OUD persons and including pain outcomes, two studies described evidence of analgesic effects (49, 50) and one did not (see Table 4. Glial Activation Inhibitors) (51). The co-administration of ibudilast and oxycodone produce an additive analgesic effect in two double-blind randomized controlled trials, consistent with results from rodent studies (52). However, these positive studies have shown inconsistent findings across different pain scales and doses of glial activation inhibitors. Moreover, the negative study (51) had several limitations, such as lack of a healthy control group , a small sample size, and a brief treatment duration, which collectively may have precluded the ability to detect small but clinically meaningful effects. All three studies provided evidence of a favorable safety profile, with minimal adverse effects and no serious adverse effects.

In sum, although glial cell activation can affect both pain and reward pathways, more comprehensive clinical trials are needed to evaluate the analgesic efficacy of glial activation inhibitors in opioid-dependent individuals. Their ideal dosage, treatment duration, and effects on opioid abuse potential have not been determined. Nonetheless, the promising preclinical and early human data suggests that these drugs have considerable potential for pain management in individuals with OUD.

3.5 Cholecystokinin Antagonists

The hormone Cholecystokinin (CCK) was initially identified as a modulator of digestive function. However, subsequent research described CCK receptors in both the peripheral nervous system and the CNS, potentially blocking the action of the endogenous opioids (53). Further, animal studies have shown that endogenous CCK is necessary for morphine reward and CCK receptors are upregulated after chronic morphine treatment (54, 55). These findings rendered CCK antagonists a potential therapy for patients who exhibit poor response to opioid treatment due to high levels of tolerance, severe adverse effects, or opioid-induced hyperalgesia.

A prospective, double-blind crossover trial evaluated the efficacy of proglumide — a nonspecific CCK antagonist previously used to treat peptic ulcers before the availability of H2 antagonists — as an adjuvant treatment to patients with chronic pain on LTOT. The study found that proglumide increased the analgesic effect of morphine in opioid-dependent patients (see Table 5. Cholecystokinin Antagonists) (56). Proglumide was also effective as an opioid agonist when given to patients with intractable pain (57). Pain perception of patients who received a full analgesic morphine dose plus placebo was equivalent to those who received half analgesic dose plus 50 mg proglumide. Both trials indicated that the drug was well tolerated, without severe adverse effects (56, 57).

However, a subsequent double-blind crossover study that examined the effects of L-365,260, a selective CCK1 antagonist, in patients with chronic neuropathic pain failed to improve morphine analgesia, despite previous rodent literature indicating a more dominant role of

the CCK1 receptors than the CCK2 receptors for opioid analgesia. The author argued that the localization and importance of each of these receptors may vary between species, underscoring the need for further research to understand the link between CCK antagonists and opioid tolerance in humans (58).

Despite the wealth of preclinical studies supporting the importance of CCK receptors for the rewarding effects of opioids and opioid-seeking behavior, no human studies have investigated CCK antagonists as a treatment for patients with OUD. These findings highlight the need for further research to fully understand the potential of CCK antagonists for patients with OUD.

3.6 NMDA Antagonists

Glutamate is a major excitatory neurotransmitter that mediates both peripheral and central pain (59). The ionotropic (AMPA, NMDA, and kainite) glutamate receptors are found throughout the nervous system and play a key role in central sensitization, reward, and aversion. The modulation of NMDA-type receptors with antagonists such as ketamine has long composed multimodal pain management strategies and appears in consensus pain guidelines as a stand-alone option alongside concurrent treatment (60). The NMDA-receptor antagonism in the brain and spinal cord (61) is thought to be the mechanism by which ketamine inhibits morphine tolerance and dependence, as well as fentanyl-induced hyperalgesia (62–64). Ketamine has been explored to decrease OIH and curb the opioid requirement post-surgery (65, 66), as well as used in the treatment of cancer pain (67), non-cancer chronic pain (68), and chronic neuropathic pain (69). Dextromethorphan, other NMDA antagonists, have been investigated to treat pain in individuals with opioid dependence (70).

Randomized controlled trials of ketamine among opioid-dependent individuals have primarily focused on post-operative pain management and opioid use outcomes (see Table 6. NDMA Antagonists and Appendix 2, Supplementary Material). While some evidence supports ketamine’s efficacy in this context, there are also negative studies (71). Most studies investigated the use of IV ketamine infusions during or after surgery, with only one study administering oral ketamine for neuropathic pain in the outpatient setting (72). Collectively, these studies enrolled diverse patient samples, used different surgical indications, and varied in the type of opioid, administration route, and treatment duration, which hinder broad generalizations.

In addition, retrospective studies examined low-dose ketamine infusions in women with OUD after cesarean delivery (73), individuals on LTOT for chronic pain (74), or complex regional pain syndrome (75). Ketamine reduced pain and opioid use among patients receiving palliative care or experiencing cancer-related pain, which is often refractory to opioid treatment (38, 76–81).

Dextromethorphan, an NMDA receptor antagonist, has been used in experimental pain studies in patients with OUD maintained on methadone (70). This experimental study failed to prove dextromethorphan-induced pain relief in OUD patients receiving methadone (see Table 6. NDMA Antagonists). Apart from this one study included in this review,

dextromethorphan has also been studied in cancer (82), fibromyalgia (83), and postoperative pain with mixed results (84).

Previous reviews have examined the potential of ketamine in the treatment of substance use disorders (85, 86). Two trials showed promising results with the use of ketamine-assisted psychotherapy to promote opioid abstinence but did not include pain-related outcomes (87, 88). Future research could explore the feasibility and potential benefits of combining psychotherapies with ketamine for both pain management and OUD. Several case studies reported the use of co-delivered ketamine and cognitive-behavioral therapy (CBT) for opioid tapering (89), as well as other case series involving comorbid PTSD and pain (90), as reviewed previously (69).

In summary, ketamine shows promise in managing pain among individuals with opioid dependence. However, further research is warranted to determine the effectiveness of other NMDA antagonists. Dextromethorphan has limited and negative results for pain management in this population. Current use in multimodal pain management regimens renders ketamine a viable approach for managing pain in those with OUD. Still, safety and abuse liability concerns in less-controlled settings must be addressed. Further research is needed to determine optimal dosing protocols and criteria for patient selection. Nonetheless, NMDA receptor modulation holds promise to manage pain in those with opioid dependence, but integration into pain management strategies for this group remains an essential question for clinicians, who must weigh the benefits and risks of these medications.

3.6 Cannabinoids

The endogenous opioid and cannabinoid systems have substantial overlap in signaling pathways that are crucial to control both pain and reward. Mounting evidence from preclinical studies suggests that cannabinoids may be effective in reducing pain, as well as curbing opioid-seeking behavior. For instance, a meta-analysis of animal studies showed that the co-administration of delta-9-tetrahydrocannabinol (THC) with opioid agonists reduced the opioid dose required for antinociception by up to nine times (91). Other preclinical studies indicate that cannabinoid agonists can attenuate opioid self-administration (92).

Although there has been substantial experimental research examining the analgesic effects of cannabinoids and its constituent cannabinoids in humans, thus far, few studies investigated the effects of cannabinoids among opioid-dependent persons — and even fewer studies included pain outcomes. Among the five human laboratory studies co-administering cannabis/THC and opioids to healthy (i.e., non-opioid dependent) persons, three studies found evidence of analgesic effects of cannabinoids on experimental pain outcomes (93–95) and two did not (96, 97). Only two randomized, placebo-controlled human laboratory studies administered cannabis or THC to persons who were already opioid-dependent (mean daily LTOT dose of 68 morphine milligram equivalents (MME) to 154 MME (98, 99), and both studies reported modest THC-induced analgesia on clinical, rather than experimental pain outcomes (see Table 7. Cannabinoids).

The nonhedonic cannabidiol (CBD), which has received FDA approval for treating rare forms of epilepsy, has demonstrated antihyperalgesic and analgesic properties in

various preclinical models of pain (100, 101). Both preclinical and human studies have suggested that CBD may reduce opioid craving and relapse (102), but the analgesic and antihyperalgesic efficacy of CBD among opioid-dependent persons have yet to be systematically investigated among persons with OUD. Ongoing clinical trials evaluate the safety and efficacy of plant-based cannabinoids, including THC and CBD, for alleviating pain among persons with OUD (103–105).

In summary, while the endogenous opioid and cannabinoid systems share important signaling pathways for pain control and reward, further research is needed to fully establish the safety profile and analgesic potential of THC, CBD, and other cannabinoids in humans with OUD. It remains to be established whether the risk/benefit ratio (e.g., the trade-off between analgesia and abuse potential and other adverse effects) of cannabinoids is favorable among this population. Nonetheless, the promising preclinical and early human data suggest that cannabinoids may hold significant promise for treating pain among persons with OUD.

3.7 Cholinergic Drugs

The cholinergic system plays an important role in the modulation of pain and reward and is a target for developing non-opioid therapeutics for pain and OUD (18). Cholinergic agonists, acetylcholinesterase inhibitors, and cholinergic antagonists have shown therapeutic potential in human studies.

Convergent studies indicate that cholinergic agonists activate cholinergic receptors in the central and peripheral nervous system, resulting in antinociception. However, their clinical use has been limited due to the undesirable adverse effects (e.g., dry mouth, excessive salivation, and sweating) resulting from the non-specific activation of cholinergic receptors. Advances in our understanding of the molecular biology of cholinergic receptors have enabled the development of agents that selectively target specific receptor subtypes, thereby improving their therapeutic potential. Nicotinic receptors are involved in modulating pain transmission and are potential targets for analgesic drug development. Recent preclinical studies have demonstrated the analgesic effects of varenicline, a partial agonist of the nicotinic $\alpha 4\beta 2$ receptor, using a rodent tonic pain model (106). However, a pilot clinical trial in patients with chronic pain using opioids did not show significant analgesic effects, although preliminary evidence showed that varenicline reduced opioid withdrawal symptoms (107). This highlights the need for further large-scale clinical trials to evaluate the therapeutic potential of varenicline in the treatment of pain and addiction-related outcomes in OUD.

Alternatively, another strategy to harness the therapeutic potential of the cholinergic system is to increase synaptic acetylcholine levels using anticholinesterase inhibitors (AChE inhibitors). Studies have shown that AChE inhibitors, such as donepezil and rivastigmine, may enhance opioid-induced analgesia and attenuate the development of tolerance to morphine's analgesic effects. Donepezil reduced opioid-induced sedation without affecting analgesia in a sample of cancer patients (n=6) that were receiving high doses of opioids (108). Additionally, a post-hoc analysis of a randomized, placebo-controlled clinical trial

indicated that galantamine may reduce nonmedical opioid use in patients with OUD who are receiving methadone maintenance (109).

Finally, the cholinergic antagonist scopolamine was tested among 91 opioid-dependent persons undergoing opioid taper. Scopolamine administration was associated with lower anxiety and depression ratings, in addition to less severe opioid craving and longer abstinence from nonmedical opioid use (110).

Taken together, these findings suggest that cholinergic drugs hold promise and should be further tested, especially in patients with comorbid OUD and chronic pain, as this population tends to require higher doses of opioid agonist maintenance but may not achieve sufficient analgesia. Further clinical trials are needed to evaluate the efficacy and safety of these drugs in different pain conditions, including chronic pain and OUD, and to identify optimal dosing regimens and potential side effects.

3.8 Serotoninergic Antidepressants

There is high comorbidity and a likely bidirectional relationship between chronic pain and depression, meaning that one condition may trigger or worsen the other (111). Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) are widely used for various pain disorders, with TCAs and SNRIs gaining prominence in the management of neuropathic and functional pain syndromes (112).

Still, our review identified only a single study that specifically investigated the effects of an antidepressant on measures of pain in a population of opioid-dependent patients on OAT (see Table 8. Serotoninergic Antidepressants). The participants were receiving buprenorphine/naloxone and experienced symptoms of depression and were randomized to receive daily oral doses of either escitalopram 10 mg or placebo. Even when adjusting for the severity of depressive symptoms, the escitalopram group experienced larger reductions in pain severity and pain interference from baseline to follow-up. Changes were statistically and clinically significant (113).

A 2017 systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of opioids combined with antidepressants or antidepressants alone versus opioids alone for different types of cancer pain was inconclusive due to a scarcity of eligible studies (26). This review also pointed out a common limitation in many clinical trials, namely the absence of a control group receiving only opioid therapy, which would aid in determining the effects of adding an antidepressant to the pain management plan of persons receiving LTOT.

Duloxetine, an SNRI, has been investigated as a potential postoperative analgesic. A 2020 systematic review and meta-analysis of randomized controlled trials found statistically significant improvements in pain and reduced opioid consumption in the first 48 hours following surgery with duloxetine, although the effect sizes did not reach clinical significance. However, the analysis was limited by high methodological heterogeneity and risk of bias, leading to a classification of very low-quality evidence

(114). Another systematic review and meta-analysis in 2021, this time focusing on elective orthopedic surgeries, demonstrated that perioperative use of duloxetine significantly reduces postoperative opioid intake (115).

It is noteworthy that our search yielded only one publication addressing the use of antidepressants for the management of OIH: a 2020 case report detailing a 58-year-old palliative cancer patient who experienced a reversal of opioid-induced allodynia and hyperalgesia, along with improved pain control and marked reductions in opioid requirements after initiating and titrating duloxetine (116).

In conclusion, current research has yet to provide a complete understanding of the therapeutic implications of antidepressant use for pain management in chronic opioid users. As effective antineuropathic agents, SNRIs and tricyclics warrant further investigation in larger, more rigorous studies targeting OIH and acute pain management among chronic opioid users, ideally with an experimental pain component.

3.9 Serotoninergic Psychedelics

Psychedelics have gained attention as a potential treatment for chronic pain management. Recent reviews have highlighted the proposed mechanisms of “classic” psychedelics, such as psilocybin and LSD, in chronic pain modulation (117–119). The activation of the 5-HT2A receptor by these substances may be responsible for their effects on pain perception, affective processing, and other positive changes in health behaviors, mood, and pain beliefs (120–124). Moreover, preclinical studies have suggested that psychedelics may also possess anti-inflammatory properties, which could contribute to their analgesic effects (125, 126).

While limited data is available from clinical studies to determine the role of psychedelics in the management of pain in those with opioid dependence, some parallels can be drawn with the literature on psychedelics for OUD. Early studies on the utility of LSD for OUD were promising (127, 128), and more recent studies have primarily focused on ibogaine and noribogaine for opioid withdrawal and use disorder (129–138). Moreover, a single study has investigated the use of ayahuasca, a traditional Amazonian decoction which contains beta-carboline alkaloids and N,N-dimethyltryptamine (DMT) (139, 140), for OUD (141). National survey data and other studies on naturalistic psychedelic use have indicated a decrease in opioid use and risks of OUD (142–145).

While LSD has been investigated for its analgesic effects in patients without opioid dependence (146–148) its potential use in pain management for terminal illness and cancer patients, in particular, has been more extensively studied (149–151). Recent experimental studies in healthy volunteers have shown positive results for LSD’s analgesic effects (152). Nevertheless, the use of psychedelics for pain management is still in its early stages, and more research is required to characterize their role in opioid-dependent individuals and in different pain treatment modalities. Additionally, the possible risks versus benefits of psychedelic treatment and their effects on OUD warrant further investigation. Despite this, the limited available data suggest that psychedelics may hold promise for pain management and should be explored further.

4. Discussion

Our comprehensive literature review has identified several potential non-opioid pharmacological approaches for pain management in opioid-dependent individuals. Ketamine, gabapentinoids, and antidepressants have been widely tested as adjunctive analgesics to opioids in human studies, focusing on perioperative analgesia and intractable cancer pain. The primary outcomes in these trials have been visual and numerical pain intensity rating scales and opioid consumption. However, the number of studies that have used experimental pain measurements is limited, and investigations have included the drugs mentioned above, as well as cannabinoids and glial activation inhibitors. Notably, our search did not yield any experimentally evoked pain studies examining the use of cholinergic drugs, alpha-2 agonists, or CCK antagonists. These findings offer important methodological, clinical, and mechanistic implications for pain management in opioid-dependent individuals.

4.1 Methodological Implications

Despite the high prevalence of comorbid OUD and pain syndromes, a limited number of interventional clinical studies have investigated pain management strategies specifically in this population. The few studies that explored non-opioid pharmacological analgesia in patients on OAT are characterized by small samples and highly heterogeneous patient population. Studies often fail to report the precise duration of opioid treatment, baseline opioid dose, and OUD severity of patients. Further, the trials conducted so far differ on the types of pain studied or include a variety of pain syndromes within the same sample. Similarly, the duration of trials and follow-ups have largely been too short to capture the effects on clinical fluctuations and relapses typical of OUD and chronic pain.

Extensive research has been conducted on add-on therapies to improve perioperative pain outcomes and opioid consumption. Still, most of this data has limited generalizability for persons receiving LTOT or with OUD. Most of these studies only included patients that were not already on opioid therapy or simply did not fully report patients' previous exposure to opioids. Furthermore, our review revealed that the majority of experimental pain studies involving individuals with OUD excluded those with chronic pain syndromes. While this approach can help to better understand the effects of opioids on pain sensitivity, it does not allow for an exploration of the interaction between pre-existing pain and opioid use.

4.2 Clinical Implications

The literature review conducted highlights a significant oversight in measures of abuse liability of potential non-opioid analgesics, such as ketamine, gabapentinoids, and cannabinoids, among individuals with OUD, despite their known abuse potential. Given that OUD is a risk factor for other substance use disorders (153), it is crucial to have a reliable risk assessment to determine the balance between analgesic benefits and potential adverse effects in individuals receiving LTOT. It is important to acknowledge that many individuals with OUD suffer from insufficient pain control, for which there is currently no tailored clinical guideline. To minimize the risk of polypharmacy, it is recommended to time adjuvant drug therapy to stages of expected pain exacerbation, such as opioid initiation, titration, taper, switch, and withdrawal. In addition, drug selection can be based on their

ability to treat additional comorbidities. Notably, many of the drugs discussed in this review have shown promise in reducing opioid requirements and improving OUD symptoms. Moving forward, as experimental pain research progresses, it may provide a valuable tool to help distinguish primary pain from pain caused or worsened by pharmacotherapy in the clinical setting.

4.3 Mechanistic Implications

Chronic opioid use alters the brain's pain processing mechanisms and the effects of medications in ways that are still not fully understood. Preclinical models of OUD typically prioritize morphine use over methadone or buprenorphine, which hinders our understanding of the pharmacodynamic and mechanistic effects of these drugs in OUD and pain management. There is a need for reverse translation studies that model comorbid OUD and pain with conventional OAT drugs to provide better mechanistic and pharmacodynamic insights. In human studies, there is a significant lack of research on pharmacokinetic interactions between opioids and commonly used co-analgesics, which limits the interpretation of the analgesic and opioid-sparing effects of these drugs. Addressing these knowledge gaps can inform better clinical management strategies for pain and OUD, particularly in cases where OATs are used.

5. Limitations

Although we reviewed a highly heterogeneous body of literature, we identified methodological discrepancies and gaps in knowledge, outlined a framework for future research, and raised awareness of a clinically overlooked topic. A crucial strength of this work is that it stems from an interdisciplinary understanding of pain and addiction at the conceptual and methodological levels. A logical progression of this review is the methodological integration of pain and addiction research tools that are capable of providing objective and reproducible findings. Future studies can build on this review to advance our understanding of non-opioid pharmacological approaches for pain management in individuals with OUD and improve clinical guidelines and treatment strategies for this vulnerable population.

6. Conclusion

In conclusion, there is a pressing need for better-designed clinical trials and human laboratory studies to investigate the potential benefits of several non-opioid analgesics in individuals on LTOT or with OUD. Although drugs such as ketamine, gabapentin, serotoninergic antidepressants, and alpha-2 agonists have shown encouraging results in clinical research, the focus of OUD has primarily been on opioid craving and withdrawal, rather than the potential pain-relieving properties of these medications in this population. As a result, their capacity to alleviate pain in individuals with OUD has been disproportionally overlooked. It is essential to correct this disparity, as pain plays a significant role in promoting and maintaining OUD, and individuals with OUD require alternatives to opioids for effective pain management. As new therapeutic options, such as psychedelics and cannabinoids, emerge as potential treatments for OUD, it is vital to thoroughly investigate their impact on pain sensitivity. The search for novel pharmacological strategies needs to

recognize the intricate neurochemical mechanisms of pain and the unmet clinical needs of individuals with OUD. Overall, the human evidence suggests that there are significant opportunities to improve pain management for individuals with OUD and highlights the need for continued research in this area as a crucial response to the escalating opioid crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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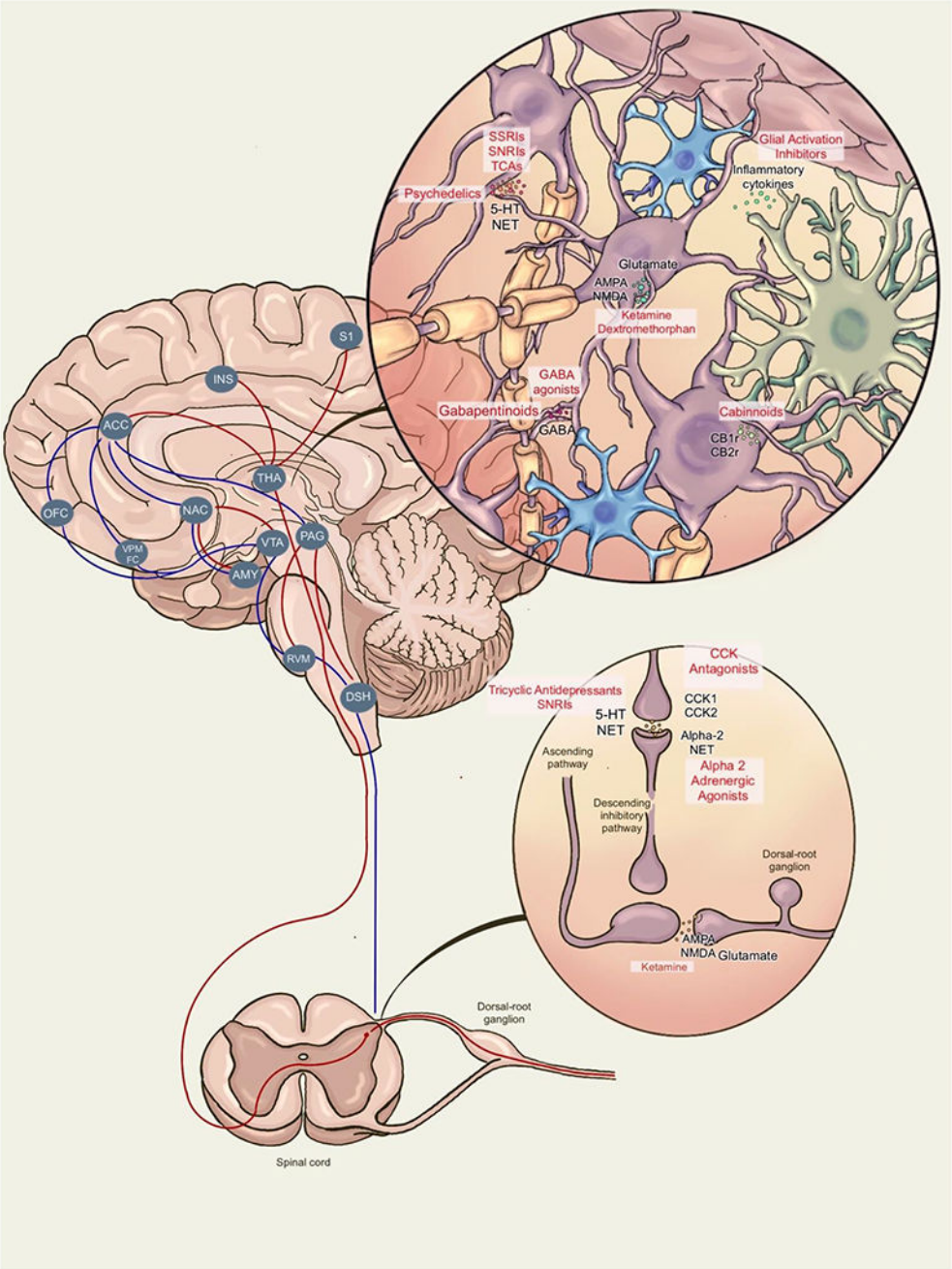

Figure 1.

The significant overlap between the neurobiological substrates of pain and reward must be considered when developing novel therapeutics for pain among persons with opioid addiction or dependence. The cortical and subcortical areas connect by ascending and descending pathways, represented by red and blue lines, respectively. The reward neurocircuitry involves various limbic and cortical brain regions, such as the ventral tegmental area (VTA), nucleus accumbens (NAC), amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (VMPFC). The

pain pathways include periaqueductal gray (PAG), rostral ventral medulla (RVM), thalamus (THA), insula (INS), VTA, NAC, ACC, the somatosensory cortex (S1), prefrontal cortex (PFC), amygdala (AMY), and dorsal horn (DSH) of the medulla (15). The illustration displays pain therapies that function within the brain and spinal cord. The targets include the facilitation of descending pain inhibitory pathway, blockade of pre- and postsynaptic receptors, and inhibition of neurotransmitter release.

Table 1.

Gabapentinoids

Study	Investigated Drugs (N)	Sample	Opioid	Pain Outcomes	Duration	Findings
Comptom et al, 2010	Gabapentin 2400mg (N=10), Placebo (N=16).	Individuals with OUD under OAT.	MethadoneN=26)	CP pain threshold and tolerance pre- and post-treatment.	5 weeks.	Gabapentin significantly improved CP pain threshold and tolerance at both peak and trough methadone levels.
Murnion et al, 2020	Gabapentin 600mg, Oxycodone IR[a], Standard OAT, Increased[b] Standard OAT (Within-subject, N=17)	Individuals with OUD under OAT.	Methadone (N=9), Buprenorphine(N=8)	CP pain threshold and tolerance	Single dose of each condition.	No improvement in analgesia compared with the control.

CP: Cold Pressor. IR: Immediate Release. OAT: Opioid Agonist Therapy. OUD: Opioid Use Disorder.

[a]Dose calculated to be equivalent to 30% of usual opioid agonist therapy.

[b]30% increase in standard opioid agonist therapy.

Table 2.

GABA Agonists

Study	Investigated Drugs (N)	Sample	Opioid	Pain Outcomes	Duration	Findings
Afzalimoghaddam et al, 2016	IM Midazolam + Haloperidol (N=43), IV Morphine (N=44).	Individuals with OUD admitted to the ED with pain.	NA	Pain intensity (NRS) and total dose of morphine	Single dose.	The Midazolam + Haloperidol group had a faster decrease in NRS scores, and lower morphine consumption compared to the morphine group.

ED: Emergency Department. IM: Intramuscular. IV: Intravenous. NA: Not available. NRS: Numerical Rating Scale. OUD: Opioid Use Disorder.

Table 3.

Alpha-2 Adrenergic Agonists

Study	Investigated Drugs (N)	Sample	Opioid	Pain outcomes	Treatment Duration	Findings
Farsani et al., 2021	Dexmedetomidine (N=30), Morphine (N=30)	Individuals with OUD undergoing cataract surgery.	NA.	Pain intensity (VAS) and analgesic request.	Single dose	Morphine group showed significantly lower pain intensity than the dexmedetomidine group during the recovery period.

NA: Not Available. OUD: Opioid Use Disorder. VAS: Visual Analog Scales.

Table 4.

Glial Activation Inhibitors

Study	Investigated Drugs (N)	Sample	Opioid	Outcome	Duration	Findings
Cooper et al, 2017	Ibudilast 20mg BID PO (N=11), Ibudilast 40mg BID PO (N=10), Placebo 0mg BID PO (N=10),	Individuals with OUD.	Oxycodone (0, 25, 50mg per 70kg PO)	Subjective (SF-MPQ) and experimental pain (CPT) measures.	2 weeks.	Oxycodone produced greater analgesia in the 40 mg BID ibudilast group compared to placebo group.
Metz et al, 2017	Ibudilast (0, 50mg BID PO), Placebo (0 mg, BID PO), (Within-subject, N=11)	Individuals with OUD not on OAT.	Oxycodone (0, 15, 30mg per 70kg PO)	Subjective (DEQ, ARCI, SOWS) and experimental pain (CPT, pain Intensity, and bothersomeness VAS) measures.	5-6 days.	Ibudilast enhanced oxycodone-induced analgesic effects compared with placebo, but findings were inconsistent between different scales.
Arout et al., 2018	Minocycline 200mg PO (N=10), Placebo(N=10).	Individuals with OUD on OAT.	Methadone or buprenorphine/ naloxone.	Subjective (POMS, BPI-SF, SF-MPQ,SOWS,) and experimental pain measures (CPT).	2 weeks.	Minocycline did not change subjective pain severity, pain threshold and tolerance for pain in the CPT.

ARCI: Addiction Research Center Inventory. BID: Twice a day. BPI-SF: Brief Pain Inventory Short Form. CPT: Cold Pressor Test. DEQ: Drug Effects Questionnaire. OAT: Opioid Agonist Therapy. OUD: Opioid Use Disorder. PO: Per Oral/Orally. SF-MPQ: Short-Form McGill Pain Questionnaire. SOWS: Subjective Opioid Withdrawal Scale. VAS: Visual Analog Scales.

Table 5.

Cholecystokinin Antagonists

Study	Investigated Drugs (N)	Sample	Opioid	Pain outcomes	Duration	Findings
McCleane et al., 1998	Proglumide 400mg, Placebo, (Within-subject, N=24)	Individuals with chronic neuropathic pain on LTOT.	Sustained-release morphine (MST)	Pain (VAS) and mobility scores.	Treatment: 2 weeks. Placebo:2 weeks.	Proglumide caused a small reduction in VAS scores compared to the placebo. Small increase in VAS scores among patients changing from proglumide to placebo.

LTOT: Long-Term Opioid Therapy. VAS: Visual Analog Scales.

Table 6.

NDMA Antagonists

Study	Investigated Drugs (N)	Sample	Opioid	Pain Outcomes	Duration	Findings
Sahmeddini et al., 2019	Ketamine (N=60), Lidocaine (N=60), Placebo (N=60).	Individuals with OUD undergoing orthopedic surgery.	Natural/ semisynthetic alkaloids.	Postop. pain intensity (NRS) and morphine consumption.	Intraop.	Lidocaine group reported lower postop. NRS and less morphine consumption on the 1st postop. day than ketamine and placebo groups. Ketamine group consumed less morphine on the 1st postop. day than the placebo group.
Rigo et al., 2017	Ketamine (N=14), Methadone (N=14), Ketamine + Methadone (N=14).	Individuals with neuropathic pain refractory to therapy.	NA.	Pain intensity (VAS).	3 months.	Ketamine group had a significant improvement in pain compared with both the methadone and methadone + ketamine groups.
Dahi-Taleghani et al., 2014	PCA Ketamine + Morphine (N=70), PCA Placebo + Morphine (N=70).	Individuals with OUD.	Opium.	Postop. pain intensity (VAS) and rescue analgesia consumption.	Postop.	Ketamine + Morphine group reported lower postop. VAS and required less postop. analgesia.
Compton et al., 2016	DEX (N=18), Placebo (N=12).	Individuals with OUD and OIH.	Methadone.	Experimental pain (CP and ES) measures.	5 weeks.	No difference between groups on CP pain threshold, CP pain tolerance, ES pain threshold, or ES pain tolerance, both pre- and post-medication.

CP: Cold Pressor. DEX: Dextromethorphan. ES: Electrical Stimulation. NRS: Numeric Rating Scale. PCA: Patient-controlled Analgesia. OIH: Opioid-induced Hyperalgesia. OUD: Opioid Use Disorder. VAS: Visual Analogic Scale.

Table 7.

Cannabinoids

Study	Investigated Drug (N)	Sample	Opioid	Pain Outcomes	Duration	Findings
Narang et al, 2008	1ST phase: Dronabinol (10, 20 mg PO) (N=30) 2nd phase: Dronabinol 5-60mg per day	Individuals with chronic pain and opioid dependence (> 6 months).	Various opioid analgesics (e.g., oxycodone, hydrocodone)	Pain intensity (VAS) prior to and relief for 8hr post-treatment.	1ST phase[a]: 2nd phase[b]: 4 weeks.	1ST phase: both 10 and 20 mg of dronabinol groups showed a small magnitude reduction in pain scores compared to the placebo. 2nd phase: modest reduction in mean pain intensity ratings.

PO: Per oral/Orally.

[a] 1ST phase: randomized, crossover, placebo-controlled study.

[b] 2nd phase: open-label extension of 1ST phase.

Table 8.

Serotoninergic Antidepressants

Study	Investigated Drugs (N)	Sample	Opioid	Pain Outcomes	Duration	Findings
Tsui et al, 2011	Escitalopram 10mg (N=72), Placebo (N=75).	Individuals with OUD and depressive symptoms starting OAT.	Buprenorphine	Pain severity (VAS) and interference (BPI).	3 months.	Escitalopram significantly improved pain severity and interference during treatment period.

BPI: Brief Pain Inventory. VAS: Visual Analog Scales. OAT: Opioid Agonist Therapy. OUD: Opioid Use Disorder.