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**Review Article**

# Pharmacological and Herbal Treatments, Cognitive Behavioral Therapy, and Combined Approaches in Opioid Use Disorder: A Narrative Review

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**Abstract**
Addiction to narcotics, also known as opioid use disorder, brings extensive harm and challenges to the patient and society. Therefore, researchers have continually sought to find more effective protocols for treating this disorder. Pharmacological treatments have long been used for this purpose. In addition, the effectiveness of psychotherapies, specifically cognitive behavioral therapy (CBT), has always been reported in this regard. Accordingly, the present study focused on reviewing the existing findings in the mentioned field. To this end, reputable scientific databases were searched using selected keywords. The extracted findings were analyzed, categorized, and then edited in several stages. The obtained data demonstrated the efficacy of pharmacotherapy as a cornerstone of care for opioid-dependent patients. On the other hand, the findings revealed that the maintenance of treatment requires the prescription of psychotherapy, especially CBT. Therefore, the combined use of these two therapeutic approaches, in addition to the short-term effect, will also lead to long-term care for the patient. Given that controlling opioid dependence has considerable economic benefits for societies, designing and testing various combination protocols can be extremely cost-effective.
**Keywords:** Opioid use disorder, Addiction, Cognitive behavioral therapy, Combination therapy

## Introduction

The systematic control of substance use disorders, particularly among young people, is a serious concern due to the health, economic, and social burden it places on societies.[1] Accordingly, opioid use disorder (OUD) remains a severe public health challenge, characterized by high relapse rates, substantial social and economic burdens, and profound individual consequences (e.g., tolerance and dependence).[2-5] Recent evidence indicates that relapse rates during the first year of treatment are high among individuals with opioid use disorder, highlighting the urgent need for effective, sustained, and reliable therapeutic strategies.[6] Beyond healthcare costs, OUD significantly impacts the quality of life, occupational functioning, and interpersonal relationships, thereby emphasizing the importance of comprehensive interventions.[7,8]

Pharmacological treatments, particularly opioid agonists (e.g., methadone and buprenorphine), constitute the cornerstone of OUD management. Methadone, a μ-opioid receptor (MOR) agonist, demonstrates superior efficacy in retaining patients in treatment and reducing illicit opioid use, though its complex pharmacokinetics necessitate careful monitoring.[9] Buprenorphine, a partial MOR agonist, also reduces cravings and opioid use while providing a ceiling effect and lower abuse potential. Depot injections allow for extended dosing intervals, thereby improving adherence while reducing diversion risks.[10] Naloxone, a pure MOR antagonist, acts by rapidly and competitively displacing opioids from their receptors.[11] The combination of buprenorphine with naloxone further mitigates the risk of diversion while maintaining therapeutic effectiveness. Although complementary herbal medications have been explored, current evidence remains limited, suggesting potential adjunctive benefits.[12]

Cognitive behavioral therapy (CBT) is an essential psychosocial intervention for OUD. By addressing maladaptive thoughts and behaviors, CBT enhances

motivation, improves adherence, and reduces relapse risk.[13] The integration of CBT with pharmacotherapy, particularly in group-based formats, significantly improves treatment outcomes compared to medication alone. Individual CBT, however, demonstrates lower efficacy, emphasizing the need for patient-tailored approaches that consider opioid type, comorbidities, and contextual factors.[14]

Combined approaches (integrating pharmacotherapy and CBT) have shown the highest promise in sustaining abstinence and improving treatment retention. Based on randomized controlled trials, patients receiving both interventions have markedly higher completion rates and longer durations of opioid abstinence than those receiving single-modality treatment.[15] These findings indicate the necessity of addressing both physiological and behavioral components of addiction to optimize long-term recovery.

Given the substantial burden of OUD and the evidence supporting multimodal interventions, this narrative review aims to examine the current literature on pharmacological treatments, herbal interventions, CBT, and their combined application, thereby providing a comprehensive understanding of effective strategies for managing OUD. Figure 1 represents a schematic theme regarding the goals of the present article.

## Pharmacological Treatments

In addition to their analgesic effects, opioids have a wide variety of consequences on the body, such as dependence, tolerance, constipation, and respiratory depression, many of which are mediated through μ receptors.[2-5,16] The most frequent method of treating OUD is medication with agonists.[17] Full MOR agonists produce robust receptor activation, suppress opioid withdrawal by occupying MOR and restoring opioid signaling, and reduce illicit opioid use through sustained receptor-mediated effects. These actions confirm the effectiveness of methadone in OUD treatment.[18,19] Partial μ-agonists produce submaximal receptor activation and relieve withdrawal and craving while imposing a ceiling on respiratory depression and euphoria, thereby increasing safety and accessibility. Buprenorphine exemplifies this profile and supports office-based treatment and lower overdose risk compared with full agonists.[18,20] A competitive MOR antagonist such as naloxone rapidly displaces opioid agonists from MOR.[21] Each pharmacotherapy will be reviewed in the following sections.

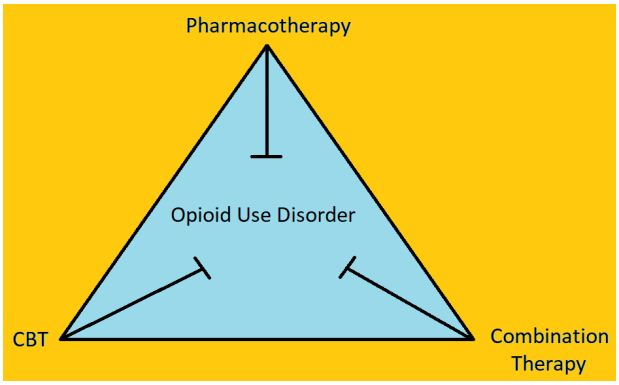


**Figure 1. Important therapeutic approaches to opioid use disorder**
*Note*. CBT: Cognitive behavioral therapy

### Buprenorphine

Buprenorphine has been known as a partial agonist for MORs with high receptor affinity and slow dissociation; these properties allow this agonist to displace full opioid agonists while producing a ceiling effect on respiratory depression and euphoria.[17,22,23] Clinically, these pharmacodynamic features translate into reduced cravings, lower rates of illicit opioid use, and a comparatively favorable safety profile versus full agonists.[24-26] Buprenorphine is available in multiple formulations, including sublingual, transdermal, and long-acting depot injections, thereby enabling flexible dosing strategies that may improve adherence while reducing diversion.[10,23,27] Its slow receptor dissociation prolongs clinical activity and supports once-daily or long-acting depot dosing.[28] Pharmacokinetically, although it is primarily metabolized hepatically to an active metabolite with relatively predictable kinetics, drug interactions and hepatic impairment remain important considerations, and this is an advantage to reduce the rate of toxification.[29-31] Compared with methadone, buprenorphine has advantages in safety but has mixed evidence regarding treatment retention, particularly at lower doses.[32]

### Methadone

Methadone is a popular agonist for MORs with a delayed onset and prolonged elimination half-life. It can produce physiological dependence without necessarily provoking destructive behaviors. Generally, it has less disruptive effects on mood, judgment, and psychomotor performance compared with some other opioids.[22,33] Reported plasma half-lives are highly variable, spanning approximately 5–130 hours, which complicates the prediction of peak concentrations and clinical effects.[34,35] Methadone appears to stabilize MOR conformations that differ from those favored by classical opioids or G protein-biased agonists, but the clinical consequences of these conformational differences remain unclear.[36-38] Moreover, plasma protein binding influences methadone pharmacokinetics. Further, alpha-1-acid glycoprotein concentrations increase in alcohol dependence and, according to some studies, in heroin addiction as well. The free fraction, distribution, and pharmacologic activity of methadone can be altered by binding to alpha-1-acid glycoprotein and other plasma proteins.[39] After oral administration, methadone is well absorbed and measurable in plasma within 15–45 minutes.[33] Additionally, its hepatic metabolism is primarily mediated by cytochrome P450 enzymes, thereby producing multiple metabolites and interindividual variability in clearance.[40] This pharmacokinetic diversity necessitates careful, individualized dose titration in order to avoid accumulation, toxicity, or subtherapeutic exposure.[34,35]

Pharmacodynamically, the combined μ-opioid agonism and partial N-methyl-D-aspartate receptor antagonism of methadone contribute to its efficacy for both nociceptive and neuropathic pain and may mitigate the development of opioid tolerance. Clinical trials and network meta-analyses have consistently confirmed that methadone outperforms many alternative pharmacotherapies for OUD in the retention of treatment and a reduction in illicit opioid use. Nonetheless, these benefits are dose-dependent and require close monitoring because of risks such as overdose, heart rate-corrected QT prolongation, and diversion.[9,34,39,41,42]

## Naloxone

Naloxone, a pure MOR antagonist, is a critical and life-saving intervention for acute opioid overdose. Unlike agonist treatments (methadone and buprenorphine) that manage chronic OUD, naloxone functions by competitively and rapidly displacing opioids from their receptors, resulting in almost immediate reversal of the central nervous system and respiratory depression.[11]

Due to this urgent action, it is considered an essential component of the overall OUD treatment landscape, focusing on reducing harm and preventing mortality.[43]

The pharmacological profile of naloxone is characterized by a high binding affinity for the MOR, exceeding that of most full agonists, but a short plasma half-life (approximately 30–81 minutes). This short half-life is a crucial clinical consideration, as patients who have taken long-acting opioids (e.g., methadone or extended-release formulations) may experience the recurrence of respiratory depression after the initial reversal effect has worn off. Consequently, all patients receiving naloxone require immediate and sustained medical monitoring.[44,45]

A serious clinical challenge of naloxone administration is the potential to precipitate acute and severe opioid withdrawal symptoms.[46] While this effect confirms the drug's efficacy, it can result in patient agitation, refusal of further medical care, or immediate departure from the scene. Therefore, its use must be followed by patient counseling and immediate linkage to formal OUD treatment (ideally involving agonist therapy) in order to maintain engagement while preventing subsequent overdose.[11,47]

## Herbal Medication

The search for alternative therapies frequently leads individuals with OUD to use herbal medications and complementary remedies. While some traditional remedies are explored for their potential to alleviate withdrawal symptoms or reduce cravings,[5] the scientific evidence supporting their efficacy and safety in OUD is generally limited, and the regulatory oversight is often lacking.[48] It is noteworthy that the use of these products is associated with certain risks, including dependence. Considering that the regulatory status in this regard remains inconsistent globally, treatment with unstandardized herbal compounds presents its own challenges.[49]

More critically, these herbal supplements pose a serious risk of pharmacokinetic drug interactions when combined with the established OUD treatments, particularly methadone and buprenorphine. The metabolism of both agonist medications heavily relies on cytochrome P450 (CYP450) liver enzymes, primarily CYP3A4.[50] Numerous common herbal products, such as St. John's Wort (Hypericum perforatum), are potent inducers of CYP3A4. These products can rapidly increase the metabolism of methadone or buprenorphine, thereby reducing their plasma concentrations.[51] This decline can lead to sub-therapeutic medication levels, resulting in increased opioid craving, breakthrough pain, and a heightened risk of treatment discontinuation or relapse.[52] Consequently, clinicians must meticulously screen for concurrent herbal use and counsel patients on the serious risks of such undetected drug-herb interactions.[53]

## Cognitive Behavioral Therapy

CBT is a well-known method with clearly observed and reported effectiveness, to the point that it is recognized as the gold standard for the treatment of various psychiatric disorders.[54] This approach is based on the active participation and constructive collaboration of the therapist with the patient.[55] Based on the available literature, CBT can be used for treating a number of disorders, including binge eating disorder, bulimia nervosa, generalized anxiety disorder, social anxiety disorder, panic disorder, and major depression. Furthermore, strong evidence supports the effectiveness of CBT in better management of OUD.[56] In this regard, the results of a systematic review also demonstrated the effectiveness of CBT in empowering patients to better cope with the disorder. However, since the protocols used in studies vary widely, achieving an ideal setting remains a challenge. Importantly, many studies have found that the simultaneous use of psychotherapy and pharmacotherapy is a prerequisite for the optimized treatment of patients suffering from OUD.[57]

## Combined Approaches

Some studies have shown that combined treatments (psychotherapy and medication) can have highly beneficial outcomes and significantly increase the effectiveness of treatment.[58,59]

Nonetheless, the gap between evidence and real-world application in this regard remains significant. In clinical practice, access to these life-saving treatments is often constrained, leading to unacceptably low utilization rates.[60] In fact, the integration of pharmacotherapy with CBT has emerged as a compelling supplementary approach within this intricate terrain, with the possibility of resolving some of the intrinsic limitations of medication-only strategies.[61]

For instance, a recent randomized trial

reported the considerable advantages of this integrative strategy. Supplementing medication-assisted treatment with regular CBT sessions could noticeably enhance treatment retention, propelling completion rates from a paltry 8% to a commendable 56%.[15] This is not merely an incremental gain. In other words, it represents a significant leap forward in engaging the patient and obtaining successful outcomes. Similarly, a secondary analysis of a separate randomized controlled trial emphasized that among individuals primarily misusing prescription opioids, the judicious addition of CBT nearly doubled the duration of opioid abstinence when compared to medication management alone.[12] Furthermore, meta-analytic insights have brought to light the critical importance of CBT's delivery format so that when synergistically used with buprenorphine, it would show a moderate and statistically significant favorable impact on treatment outcomes. Intriguingly, single CBT did not produce similar advantages,[14] suggesting that a nuanced understanding of therapeutic modalities would be indispensable.[62]

Despite these encouraging findings, the broader scientific consensus constantly maintains that pharmacotherapy remains the indispensable cornerstone of OUD treatment. Psychotherapeutic interventions, while undeniably valuable, are best understood as playing a supportive and augmentative role, rather than a substitutive one. Collectively, the extant evidence strongly suggests that strategically incorporating CBT into agonist treatment protocols can be particularly fundamental in bolstering treatment retention and significantly improving the outcomes for specific subgroups (e.g., individuals grappling with dependence on prescription opioids). Nevertheless, these observed benefits must be interpreted with appropriate scientific caution, thoroughly considering patient-level variabilities, the specific type of opioid involved, and the intricate contextual factors that invariably shape the implementation and efficacy of therapy. In addition, each patient in every situation offers its own particular tapestry that calls for customized treatments.

## Future Perspectives

In addition to evaluating the safety and efficacy of agonist drugs, future research should thoroughly examine the impact of these treatments on patients' daily functioning. It should also investigate the role of individual backgrounds in durability and the effectiveness of the therapy. Attention to individual differences and specific populations (e.g., adolescents), as well as identification of treatment barriers, can optimize and improve the success of the treatment process.

Other priorities would include conducting long-term studies to assess the reliability of results, exploring new treatments and healthcare approaches, and developing combined treatment models. Furthermore, evaluating the efficacy of chronic pain treatment alongside pharmacotherapy (not separately) and determining the appropriate dosage and duration of CBT should be taken into consideration.

Other priorities are educating physicians, treatment team members, and emergency personnel studying the dopaminergic system, increasing public awareness, and more accurately identifying the mechanisms of treatment effects to pave the way for designing treatment plans tailored to the needs of patients.

## Conclusion

Overall, the findings revealed that psychotherapy noticeably increases the effectiveness of treatment in patients with opioid use disorder when combined with pharmacotherapy. Moreover, collected reports indicated that CBT plays a prominent role in the sustainability of the achievements of the aforementioned pharmacotherapy. Accordingly, valuable combination protocols can be designed and implemented to the point where an independent research subfield can be created in this regard. In conclusion, it seems that targeted investment in optimizing the simultaneous administration of the two treatment methods can be of fundamental help to patients and the health systems of societies.

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### Competing Interests

The authors declare they have no conflict of interests.

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