

Mechanisms of opioids and evaluation on existing therapies for addiction

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Abstract. This research explores the intricate mechanisms of opioid action and evaluates a diverse of different therapeutic approaches for in the treatment of the opioid addiction. The results show that opioids produce their effects by binding to specific receptors in the central nervous system, mainly targeting μ -opioid receptors (MORs), where this interaction leads to analgesia, euphoria, and a significant risk of addiction. In addition, this research critically examines the efficacy of different addiction therapies, such as the use of methadone, is analysed for its ability to stabilize patients and reduce withdrawal symptoms and cravings. The effectiveness of behavioural therapies, such as Contingency Management (CM), is also evaluated, emphasizing their roles in reinforcing positive behaviours and addressing the psychological aspects of addiction. The research concludes with a discussion on the integration of these therapies to create comprehensive, patient-centered treatment plans, aiming to improve long-term recovery outcomes and reduce the societal impact of opioid addiction.

1 Introduction

The opioid epidemic has emerged as one significant health crisis of the 2000s. The prescription and illicit opioid abuse have increased dramatically, leading to widespread addiction, high morbidity, and high mortality. Opioids are a well-known class of drugs with three members: natural opioids, semi-synthetic opioids, and synthetic opioids characterized by potent analgesia acting primarily on the central nervous systems and peripheral nervous system. They also relieve depression and cause mood changes, as a result, they have high potential for misuse and addiction. Understanding how opioid works is critical to developing ways of combating this epidemic.

Opioids operate by binding their ligands to specific opioid receptors found in the brain, and they are also found in spinal cord. These receptors include the μ -opioid receptors (MORs), δ -opioid receptor (DOR), κ -opioid receptor (KOR), and the non-classical nociception opioid receptor (NOP), all of which are members of the G-protein-coupled receptor family. MORs are significantly involved in the addictive properties of opioids since they are implicated in the brain reward pathways, and they play a crucial role in mediating the rewarding and addictive properties of opioids. When opioids bind to MORs, they inhibit the release of

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neurotransmitters like GABA in VTA. This inhibition increases dopamine release in the nucleus accumbens (NAc), a key component of the brain's reward system. This process strengthens drug-taking behavior and plays a role in the progression of addiction. Chronic opioid use results in neuroadaptive changes, including desensitization and downregulation of receptors within the brain, and therefore, it induces both tolerance—where higher doses are required for the same effect—and dependence. Some studies showed that phosphorylation at specific residues in MORs and DORs is pivotal in these processes, exerting an impact on receptor internalization and signaling pathways [1]. It has also been shown that opioids can enhance dopamine release in the nucleus accumbens by inhibiting GABAergic neurons in the ventral tegmental area, which normally suppress dopamine release. This increased dopamine release is associated with the euphoria and reinforcing effects of opioids, which help strengthen drug-taking behavior and add to addiction. With advanced imaging and biochemical studies, these pathways have been mapped to some extent, and vital molecular players have been identified in the process.

Much recent effort has gone into understanding the mechanism of opioids, with a desperate need to manage the global opioid crisis. The study is directed at how opioids act with brain systems to be productive in releasing pain and inducing addiction. Furthering research into these mechanisms is vitally essential for devising new interventions and treatments. By revealing the complex interplay of these two intricate systems, researchers shed light on ways to curtail the devastating toll of opioid addiction on an individual and society. Further studies will continue to focus on molecular and genetic factors and innovative therapeutic approaches to counter this enduring public health challenge. There are several effective opioid addiction therapies include methadone and buprenorphine. Although treatment has made significant headway, research is called for to help beat the existing barriers, such as side effects, and make the treatment strategies effective. Treatment of opioid dependence can have serious side effects, including depressing of breath. Breathing becomes extremely slow and superficial, which can cause breathing to stop. Patients may experience gastrointestinal discomfort, including nausea and vomiting after taking medicines like methadone. This research will examine the mechanisms of three types of opioids: morphine, heroin, and buprenorphine. As well as evaluate the existing treatments of addiction of opioids concerning the use of methadone and contingency management method.

2 Morphine

2.1 Sources of morphine

As natural opioids, morphine can be extracted from opium poppy. The seeds do not contain morphine, however, when the capsules are crushed, the seeds will be polluted by plant latex which contains morphine. Although morphine is classified as natural opioids, it can be synthesized in many ways such as using thebaine.

2.2 Exposure pathways to humans

Humans can be exposed to morphine in daily life in many ways because the *Papaver somniferum* L. plants are widely used in daily life. Poppy consumption is the most common way of morphine exposure. Although its seeds can be used to produce food and craft products as there are no opiate alkaloids, the poppy latex contains such alkaloids. Because the morphine contained in some of the poppy seeds can provide the users with a delightful mood, some individuals add poppy seeds to food and drink illegally. However, their action is dangerous. There are cases in which poppy seeds were infused into beverages and caused the

individuals who drank them to be sick and even die. Morphine is widely used in the medical field. When used as a pain releaser, it can be operated into human bodies in numerous ways. It can be administrated intravenously, intramuscularly, and subcutaneously. Because morphine can be manufactured relatively more efficiently, it is often used as a recreational drug illegally. Drug addicts usually consume morphine orally, and they also inject the morphine dissolved in water into veins, muscles, or under the skin. Snorting the crushed pills and smoking the morphine vapor are also their ways to consume morphine.

2.3 Mechanism

Morphine can interact with opioid receptors and exert its effects of analgesia by inhibiting the neurotransmitter release, modulating pain pathways, and activating brain's reward system.

2.3.1 Biding to opioids receptors

Morphine has the highest affinity towards MORs. MORs have distribution in brain, and they can also be in spinal cord. They are responsible for analgesia, euphoria, sedation, respiratory depression, and physical dependence. The morphine interacts primarily with residues in the extracellular region domains of transmembrane (TM) helices 3, 5, 6, and 7 of the MORs. The phenolics of morphine form an essential interaction with histidine (H6.52) to establish a water-mediated bridge. This interaction is part of the hydrogen bonding network of lysine (K5.39) and tyrosine (Y3.33). The ligand-binding site of MORs is made up of a balanced mixture of hydrophilic and hydrophilic residues, which can accommodate the morphine molecule. Because of the balance, MORs can bind to various ligands, including morphine. The most important feature that shows that MORs are activated is forming a salt bridge between the amine group of morphine, which is charged and aspartate (D3.32) on the MORs. The formation of a salt bridge stabilizes the morphine within the binding site and promotes receptor activation [2]. Molecular Dynamics (MD) simulations explore the MORs complex with morphine. The simulation found that the MORs and morphine bind stably. Also, it is pointed out that morphine shows high binding stability during the simulation, and this emphasizes the role of critical interactions with Asp149^{3.32}, Tyr150^{3.33}, and Lys235^{5.39} which forms hydrogen bonds with morphine and stabilize its position within the orthosteric pocket. When morphine binds to the MORs, a conserved salt bridge with Asp^{3.32} forms, and hydrogen bonds are formed between morphine and Tyr150^{3.33} and Lys235^{5.39}. The binding of morphine to MORs induces specific conformational changes, particularly in TM helices 3 and 6, which activate the receptor [2].

2.3.2 Signal transduction pathways

When morphine binds to MORs, it activates GPCR signaling pathways. Morphine inhibits adenylate cyclase activity through its action on opioid receptors, which are G- GPCRs. Upon binding to the MORs, morphine activates the inhibitory G-protein, inhibiting adenylate cyclase. This causes a decline in the production of cAMP from ATP, ultimately reducing cellular responses to various signals. Morphine interacts with prostaglandin mechanisms. One significant interaction inhibits E prostaglandins (PGE1 and PGE2) stimulation of cyclic AMP (cAMP) formation. Morphine inhibits the formation of cAMP when E prostaglandins are present. This specific inhibition does not affect the basal formation of cAMP, indicating that morphine targets the pathway activated by E prostaglandins specifically [3]. However, the inhibitory effect of morphine is stereospecific. (-)-morphine has potent analgesic effects, while (+)-morphine has much lower reactivity in binding with receptors [4].

Then, the G-protein is activated, and the GIRK channels are opened. Those channels are critical in modulating neuronal excitability and various physiological processes. GIRK channels are activated by Gi/o-coupled G protein-coupled receptors (GPCRs); this increases potassium ion flow into the cell, leading to the hyperpolarization of neurons and a subsequent decrease in cellular excitability [5]. Opioids, such as morphine, can decrease the conductance of voltage-dependent calcium channels, leading to a reduction in calcium ion influx into neurons. This results in a lower release of pain-related neurotransmitters like glutamate and substance P. Additionally, morphine increases the release of inhibitory neurotransmitters, including GABA and glycine, by inhibiting these calcium channels.

By inhibiting excitatory neurotransmitters in the central nervous system, morphine effectively reduces the perception of pain. It also enhances the release of inhibitory neurotransmitters, further contributing to its analgesic and sedative effects.

3 Heroin

3.1 Sources of heroin

Heroin, a kind of semi-synthesized opioids, can be synthesized from morphine. In the process, morphine undergoes acetylation. Acetylation involves adding an acetyl group ($\text{CH}_3\text{CO}-$) to the morphine molecule using acetic anhydride ($\text{C}_4\text{H}_6\text{O}_3$) as the acetylating agent. The acetylation process converts morphine into diacetylmorphine, commonly known as heroin. The acetyl groups ($\text{CH}_3\text{CO}-$) attach to specific hydroxyl groups ($-\text{OH}$) on the morphine molecule, altering its chemical structure.

3.2 Exposure pathways to humans

Inhalation, injection, and ingestion are the most common routes of exposure. Inhalation typically involves smoking heroin, where it is heated, and its vapors are inhaled into the lungs. Injection, often intravenous, introduces heroin directly into the bloodstream, leading to rapid and intense effects but also heightening the risk of infectious diseases and overdose. Ingestion involves swallowing heroin, which is less common but can still occur, particularly in its less pure forms.

3.3 Mechanism

3.3.1 Metabolism

There are several steps for metabolism of heroin (Fig. 1). In step1 and step2 heroin will experience deacetylation reaction and form 6-MAM and morphine with catalysts like serum-cholinesterase. Step3 is glucuronidation reaction, and morphine is reacted and M3G and M6G are produced.

Although the metabolite of heroin, morphine, can provide the effect of releasing pain, it does not mean that heroin itself does not contribute to the effects. Heroin's high lipophilicity plays a crucial role in its rapid onset of effects, which is a critical factor in its addictive potential and produces effects shortly after administration. Lipophilicity refers to a substance's ability to dissolve in fats, oils, and lipids, significantly influencing how quickly a drug can cross cell membranes, including the barrier between human blood and brain. It is a specialized barrier that shields the brain selectively from potentially dangerous substances present in the bloodstream, and nutrients can go through. Due to its high lipophilicity, heroin

can quickly diffuse through this barrier, entering the brain much faster than its less lipophilic metabolites, such as morphine. Table 1 shows the partition coefficient values (Log_w^{n-oct}) of heroin, 6-MAM, and morphine. Here, "w" means water, and "n-oct" means n-octanol as an organic solvent [6].

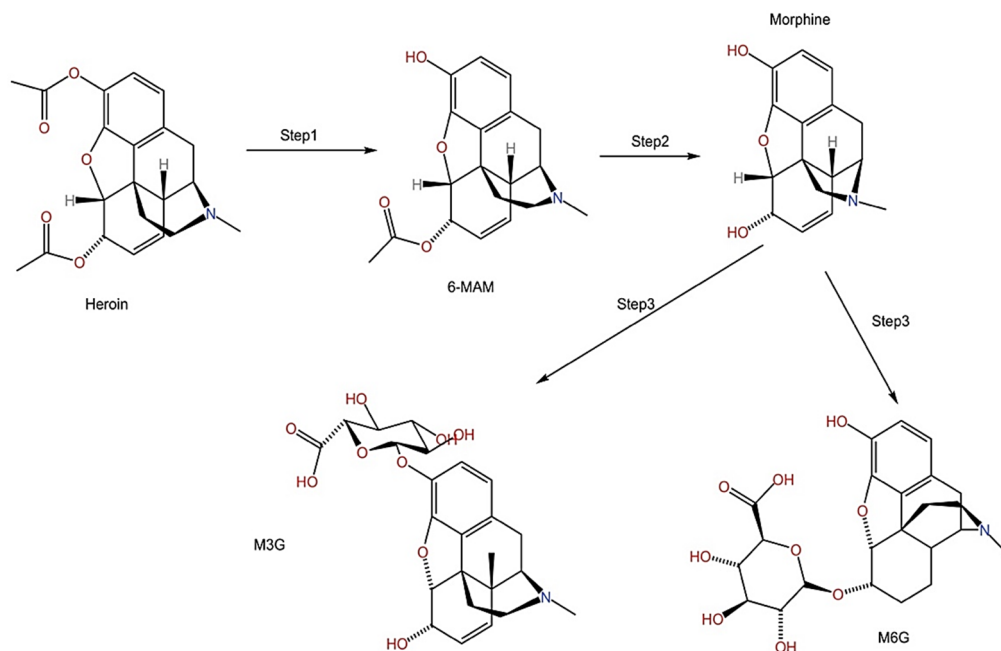


Fig. 1. Process of Heroin metabolism (Picture credit: Original).

The value of heroin is much larger than that of morphine, showing that heroin has much higher lipophilicity than morphine. The primary metabolite of heroin, 6-MAM, also has relatively high partition coefficient value, so its lipophilicity is relatively high but lower than that of heroin.

Table 1. Partition coefficient of heroin, 6-MAM, and morphine [7-9].

Compound	LogP _w ^{n-oct} of neutral molecules
Heroin	1.58
6-MAM	1.55
Morphine	-0.10

3.3.2 Biding to opioids receptors

The way that heroin and its metabolites bind to opioid receptors is similar with that of morphine mentioned in the previous paragraph. The following paragraph will discuss the difference in capacity to activate MORs through G-protein signaling pathways.

The efficacies in rat thalamic membranes and transfected C6 glioma cells expressing human MORs were examined using agonist-stimulated [35S] GTPγS binding assays [10]. 6-

MAM exhibited significantly higher efficacy in stimulating G-protein activation. This more significant effect was evident in rat thalamic membranes and human MOR-expressing C6 cells. The efficacy of 6-MAM was measured by its ability to stimulate [35S] GTP γ S binding, an indicator of G-protein activation, a critical step in the intracellular signaling cascade initiated by μ -opioid receptor activation. Heroin showed a lower potency in G-protein activation assays, primarily because it rapidly metabolizes to 6-MAM *in vitro*. This rapid conversion was confirmed through HPLC analysis, which showed that the substantial portion of heroin was deacetylated to 6-MAM when incubated with thalamic membranes. This metabolic process enhances the overall efficacy of heroin since 6-MAM, with its higher intrinsic efficacy, becomes the predominant active agent. The study's findings were further supported by the observation that naloxone, MORs antagonist, effectively inhibited the activation of G-protein induced by 6-MAM, confirming the MOR specificity of 6-MAM's actions.

Additionally, experiments with naltrindole, a DOR antagonist, showed no significant effect on 6-MAM-induced G-protein activation, reinforcing that the greater effect of 6-MAM was mediated through μ -opioid receptors rather than DOR [10]. The increased intrinsic efficacy of 6-MAM is attributed to the structural acetylation at the sixth carbon position, which enhances its interaction with MORs. This structural modification likely increases the receptor binding affinity and the efficiency of receptor activation, thereby making 6-MAM a more potent activator of the G-protein signaling pathway.

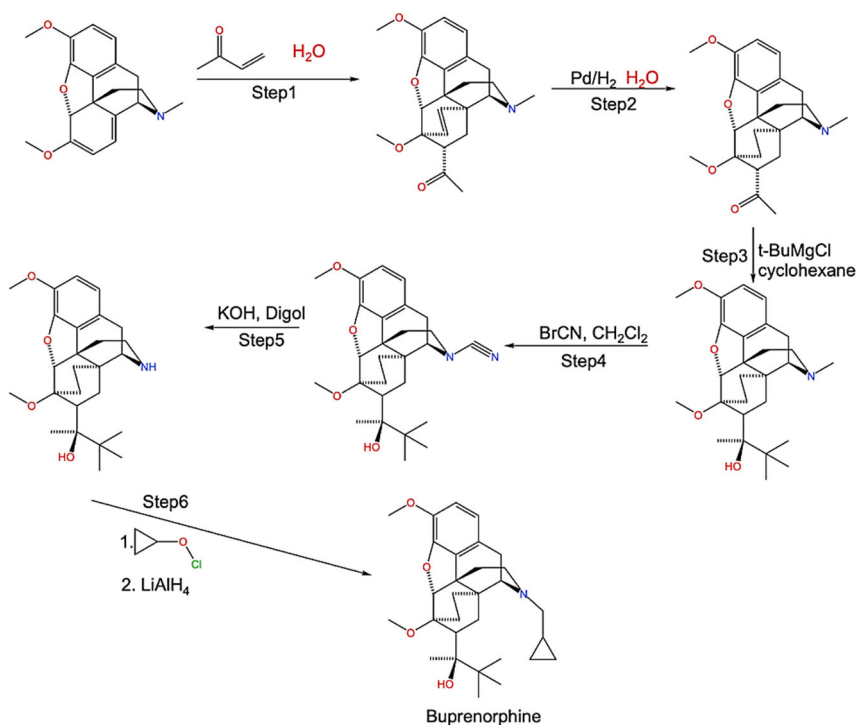


Fig. 2. Synthesis of buprenorphine [11].

4 Buprenorphine

Buprenorphine is a unique opioid with a distinct mechanism of action that sets it apart from others. It is a partial agonist at the MORs, where it binds with very high affinity, leading to potent analgesic effects. Full agonists include morphine and heroin discussed before. Unlike them, buprenorphine activates the MORs to a lesser extent.

4.1 Sources of buprenorphine

Buprenorphine can be synthesized in many ways. It can be synthesized with starting materials like thebaine. Fig. 2 shows the synthesis progresses. In step1, thebaine is reacted with acetic acid and water. Then the product is treated with hydrogen gas and water with catalyst of Pd. After that, t-BuMgCl (tert-butylmagnesium chloride) and cyclohexane is added. Then the product undergoes a cyanogen bromide-mediated von Braun N-demethylation to produce an N-nitrile intermediate. This intermediate is then hydrolyzed to form a secondary amine. The next step involves alkylation of the secondary amine with cyclopropylmethyl carbonyl chloride, followed by a reduction step using lithium aluminum hydride.

4.2 Gz protein and Ser/Thr protein phosphatases

Gz proteins are a subclass of the Gi/Go family of G-proteins, which are crucial mediators in the pathways of inhibitory signal transduction associated with GPCRs. Unlike the more widely studied Gi and Go proteins, Gz proteins are unique in their expression patterns and functional roles. They have significant characters in various physiological processes, like the modulation of neurotransmitter release, platelet aggregation, and most pertinently, pain perception. Gz proteins have been shown to be specifically involved in the drug's supraspinal effects. There is research revealed that when Gz protein expression was inhibited using antisense oligonucleotides [12], there was a significant reduction in buprenorphine-induced antinociception (Table 2).

Table 2. Effect of Gz antisense [12]

Route	Treatment*	Morphine*	Fentanyl*	Buprenorphine*
Intracerebroventricular	Control	69.0±8.9	77.2±9.1	76.3±8.8
Intracerebroventricular	Gz antisense	75.6±9.4	82.6±6.5	35.2±6.6

This reduction was not observed with other opioids like morphine or fentanyl, indicating a unique interaction between buprenorphine and Gz proteins. The exact mechanism through which Gz proteins modulate buprenorphine's effects is thought to involve the adenylate cyclase inhabitation, causing declined level of cAMP. This reduction in cAMP can alter neuronal excitability and pain signaling pathways, contributing to the overall analgesic effect of buprenorphine. The involvement of Gz proteins highlights a complex layer of regulation in opioid analgesia, distinguishing buprenorphine's mechanism from other opioids.

The same research [12] found that Ser/Thr protein phosphatases play a significant role in the drug's supraspinal antinociceptive effects. Okadaic acid, a potent inhibitor of PP2A and PP4, was used to explore this role. The administration of okadaic acid produced a biphasic effect on buprenorphine-induced antinociception: low doses attenuated the analgesic effect, while high doses enhanced it. This biphasic response was specific to buprenorphine and was not observed with other opioids such as morphine or fentanyl. The mechanism underlying this modulation likely involves the regulation of receptor signaling and downstream effectors through changes in the phosphorylation state of proteins. By inhibiting Ser/ThP phosphatases,

okadaic acid may alter the desensitization, internalization, and recycling of opioid receptors, as well as the activation of downstream signaling pathways, contributing to the distinct pharmacological profile of buprenorphine.

The combined involvement of Gz proteins and Ser/Thr protein phosphatases highlights a sophisticated regulatory network underlying buprenorphine’s analgesic effect. The specific engagement of Gz proteins suggests a distinct pathway for buprenorphine's action at the supraspinal level, separate from the traditional Gi/Go protein-mediated pathways utilized by other opioids. This pathway may involve unique receptor interactions or signal transduction mechanisms that confer buprenorphine's prolonged duration of action.

5 Therapies of addiction

5.1 The use of methadone

Methadone is a full agonist, and it has high affinity at opioid receptors, it is the most widely used medication in opioid maintenance treatment (OMT). When patients taking it orally, methadone is absorbed most entirely, and it is highly bioavailable.

In OMT, methadone administration is usually detoxified in a controlled setting firstly, and then, the dose is increased gradually, starting at 10 mg to 30 mg daily. It is important to increase the dosage slowly, ensuring the consumption is supervised, urine tests are done frequently, and regular clinical is monitored. Methadone therapy can start in both inpatient and outpatient settings, and patients may occasionally be given significantly higher doses on the first day without undergoing prior detoxification. Close monitoring during the first two hours after ingestion is important due to the potential for accumulation and synergistic effects with other sedatives and respiratory depressants, increasing the risk of mortality during the first weeks of treatment [13]. Some data was collected in China (Table 3).

Table 3. % of participants engage in drug-related criminal activities and % of participants employed in different time after being treated with methadone [13].

Routes	% participants engage in drug-related criminal activities*	% participants employed*
0	20.7	22.9
6	3.6	43.2
12	3.8	NA

As shown in Table 3, the percent of participants engage in drug-related criminal activities decreased from 20.7% to 3.8% after 12 months of treatment. The percent of people employed from 22.9 to 43.2 after 6 months of treatment. It has been proved that OMT can significantly reduce the addiction effect of opioids and help patients go back to the society again.

However, as great as it is in its benefits, it is also not free of risk or side effects. Common side effects due to methadone use are feeling lightheaded, drowsy, sick, vomiting, and constipation. Methadone also induces life-threatening respiratory depression, especially if taken in large doses concurrently with alcohol or benzodiazepines. After prolonged intake, physical dependence will be experienced, and upon abrupt cessation, withdrawal symptoms will occur. The use of methadone is associated with cardiac arrhythmia development because

of its pharmacological activity to prolong the QT interval, which can lead to life-threatening arrhythmias. Regular monitoring and careful dosing are essential to manage these risks effectively.

5.2 Contingency Management (CM)

CM is therapy differs completely with discussed before. It is a kind of behavioral and it has demonstrated significant effectiveness in the treatment of opioid addiction [14]. Grounded in the principles of operant conditioning, CM uses positive reinforcement to encourage desirable behaviors, such as abstinence from drug use and adherence to treatment protocols. By providing tangible rewards for meeting specific behavioral targets, CM aims to alter behavior patterns and support recovery. CM relies on the concept of positive reinforcement to motivate behavior change. Patients receive tangible rewards, such as vouchers, cash prizes, or other incentives, for achieving predefined treatment goals, such as negative drug tests, attendance at counseling sessions, or adherence to medication schedules. The immediacy and certainty of these rewards are crucial. They create a strong association between the desired behavior and the positive outcome, enhancing motivation and increasing the likelihood of repeated positive behavior. Clear and measurable behavioral targets are established at the outset of treatment. Common targets include regular negative urine tests for opioids and other substances, participation in therapy sessions, and compliance with medication regimens. These targets are tailored to the individual's treatment plan and are adjusted as the patient progresses through treatment. This personalized approach helps address the unique challenges and needs of each patient. CM programs often use an escalating schedule of incentives, where the value of rewards increases with each consecutive achievement of a behavioral target. This strategy not only maintains motivation but also encourages sustained engagement in positive behaviors over time. For example, a patient may receive a small reward for the first negative drug test, with the value of subsequent rewards increasing for each consecutive negative test. If a patient misses a target, the reward value may reset, but the opportunity to earn rewards remains, fostering a continuous effort toward positive behavior.

However, implementing CM requires financial resources to provide rewards and administrative support to manage the program. Securing funding and ensuring the sustainability of CM programs can be challenging, particularly in resource-limited settings. Moreover, some critics argue that providing monetary or material rewards for abstinence may be ethically questionable. Concerns include the potential for patients to become dependent on external rewards rather than developing intrinsic motivation for recovery.

6 Conclusion

Understanding the mechanisms of opioid action is crucial for developing and refining effective treatments for opioid addiction. Opioids interact with central nervous system receptors, primarily MORs, to produce their analgesic and euphoric effects, which contribute to their high potential for abuse and addiction. The involvement of Gz proteins and serine/threonine protein phosphatases in opioid signaling pathways offers deeper insights into the complexities of opioid effects and the challenges of addiction treatment. The evaluation of therapeutic approaches highlights the importance of Medication-Assisted Treatment (MAT) and behavioral therapies in managing opioid addiction. MAT, using medications like methadone provides critical support in reducing withdrawal symptoms, cravings, and the risk of relapse. Behavioral therapies, such as CM, complement MAT by addressing the psychological and behavioral aspects of addiction, reinforcing positive behaviors, and improving treatment adherence. Integrating these therapies into a

comprehensive, patient-centered treatment plan is essential for enhancing long-term recovery outcomes. The synergistic effect of combining pharmacological and behavioral interventions can significantly improve the chances of sustained sobriety and better quality of life for individuals struggling with opioid addiction. Future research should continue to explore the molecular mechanisms of opioids and innovate therapeutic strategies to address the evolving challenges of the opioid epidemic. By advancing our understanding and treatment of opioid addiction, we can reduce its devastating impact on individuals and society.

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