

Review

Chemical Neuroscience of Heterocyclic N-Amines: Implications for Pain Management, Mental Health, and Opioid Withdrawal

Ferydoon Khamooshi ^{1, *}, Samaneh Doraji-Bonjar ², Habib Ghaznavi ³, Mohammad Hasan Mohammadi ⁴, Ali Reza Modarresi-Alam ⁵, Ali Navidian ⁶, Ali Khajeh ⁷, Mohammad Kazem Momeni ⁸

1. Department of Chemistry, Faculty of Science, University of Zabol, Zabol, Iran; E-Mail: Khamooshi@uoz.ac.ir
2. Department of Laboratory Medical Sciences, Zahedan University of Medical Sciences, Zahedan, Iran; E-Mail: Doraji70@zaums.ac.ir
3. Department of Pharmacology, Zahedan University of Medical Sciences, Zahedan, Iran; E-Mail: ghaznavih@yahoo.com
4. Department of Pediatrics, Zabol University of Medical Sciences, Zabol, Iran; E-Mail: dr.mohammadimh@yahoo.com
5. Department of Chemistry, Faculty of Science, University of Sistan and Baluchestan, Zahedan, Iran; E-Mail: modaresi@chem.usb.ac.ir
6. Pregnancy Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran; E-Mail: alinavidian@gmail.com
7. Department of Pediatrics, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran; E-Mail: Dr.khajehneuro@gmail.com
8. Department of Internal Medicine, School of Medicine, Clinical Immunology Research Center, Ali Ibne Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran; E-Mail: Dr.kazemmomeni@gmail.com

* **Correspondence:** Ferydoon Khamooshi; E-Mail: Khamooshif@gmail.com

Academic Editor: Fabrizio Stasolla

Special Issue: [Pain Management and Neuromodulation](#)

OBM Neurobiology

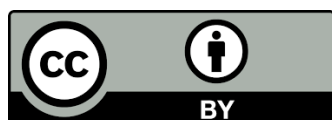
2025, volume 9, issue 2

doi:10.21926/obm.neurobiol.2502289

Received: December 05, 2024

Accepted: May 30, 2025

Published: June 10, 2025



© 2025 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

Abstract

This study reviews the biochemical mechanisms and clinical implications of N-heterocyclic amine drugs, particularly in the context of pain management, mental health, and opioid withdrawal. It highlights the structural diversity and receptor binding capabilities of these compounds, which enable them to target the nervous system and cross the blood-brain barrier effectively. The article discusses the role of opioids in pain relief, detailing their agonistic effects on opioid receptors and the subsequent risk of addiction. Furthermore, it addresses the psychological dependence that can arise from opioid use, emphasizing the need for comprehensive management strategies that include pharmacological and non-pharmacological treatments. The review also examines the biochemical changes associated with opioid withdrawal, including alterations in neurotransmitter systems that lead to symptoms such as nausea and anxiety [6]. Additionally, it presents traditional medicine approaches, such as the use of herbal remedies, as potential adjuncts in the treatment of addiction. Overall, the findings underscore the importance of understanding the chemical structures and mechanisms of these drugs to improve therapeutic outcomes in addiction and pain management. Considering the biological significance of N-heterocyclic amines due to their bioisosteric properties and the lack of such a review study, the ultimate goal of this study is to introduce and describe the pharmacological applications and biochemical effects related to the structure of this class of chemical compounds.

Keywords

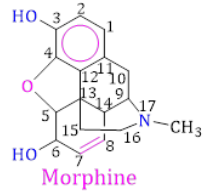
Heterocyclic N-amine drugs; dark classic in chemical neuroscience biochemistry; tetrazole; carbamate; pain chemistry; health chemistry

1. Introduction

Drugs of abuse have shaped human history for centuries. From opium dens in China during the 1800s to the cocaine and Phencyclidine (PCP) crises of the 1960s and 1970s to the current opioid and methamphetamine epidemics, society has struggled with approaches to combat illicit drugs [1]. As a scientist interested in chemistry, pharmacology, and narcotics, finding comprehensive data on the chemical structures of anti-opioid medications can be challenging. That's why we're so excited to present an extensive chemical review of the chemical structure of narcotic drugs, addictive drugs, and anti-opioid drugs under the title "Dark Classics in Chemical Neuroscience" [2-5]. An opioid is a substance that has the properties of pain relief, relaxation, anesthesia, or both. Opioids are generally divided into two categories, agonists and antagonists. Agonists mimic the effects of the body's natural opioids (such as endorphins) and produce an opioid effect by interacting with specific receptor sites in the brain. Agonists include drugs such as morphine and fentanyl, which are most commonly used in the medical field with the most potent effects [6-8]. Medicines and chemical compounds of this category have a very high possibility of abuse and addiction. Examples of other agonists are hydrocodone, oxycodone, heroin, and buprenorphine. The most common opioid agonists are listed in Table 1 [8-10]. The term "antagonist" is widely used in pharmacology and biochemistry, and it refers to a type of ligand or chemical substance

that can bind to cellular receptors or is a type of drug that binds to the receptors of a cell in the body and performs the ligand-receptor binding process, but does not cause any side effects. There is no response or reaction from the cell; in other words, they occupy the active sites of the receptor by binding to it and blocking the receptor from binding to agonists. Antagonists such as naltrexone and naloxone are less addictive than agonists. However, the potential for abuse still exists. They are often used to support the detoxification function as the first part of addiction treatment [10-13].

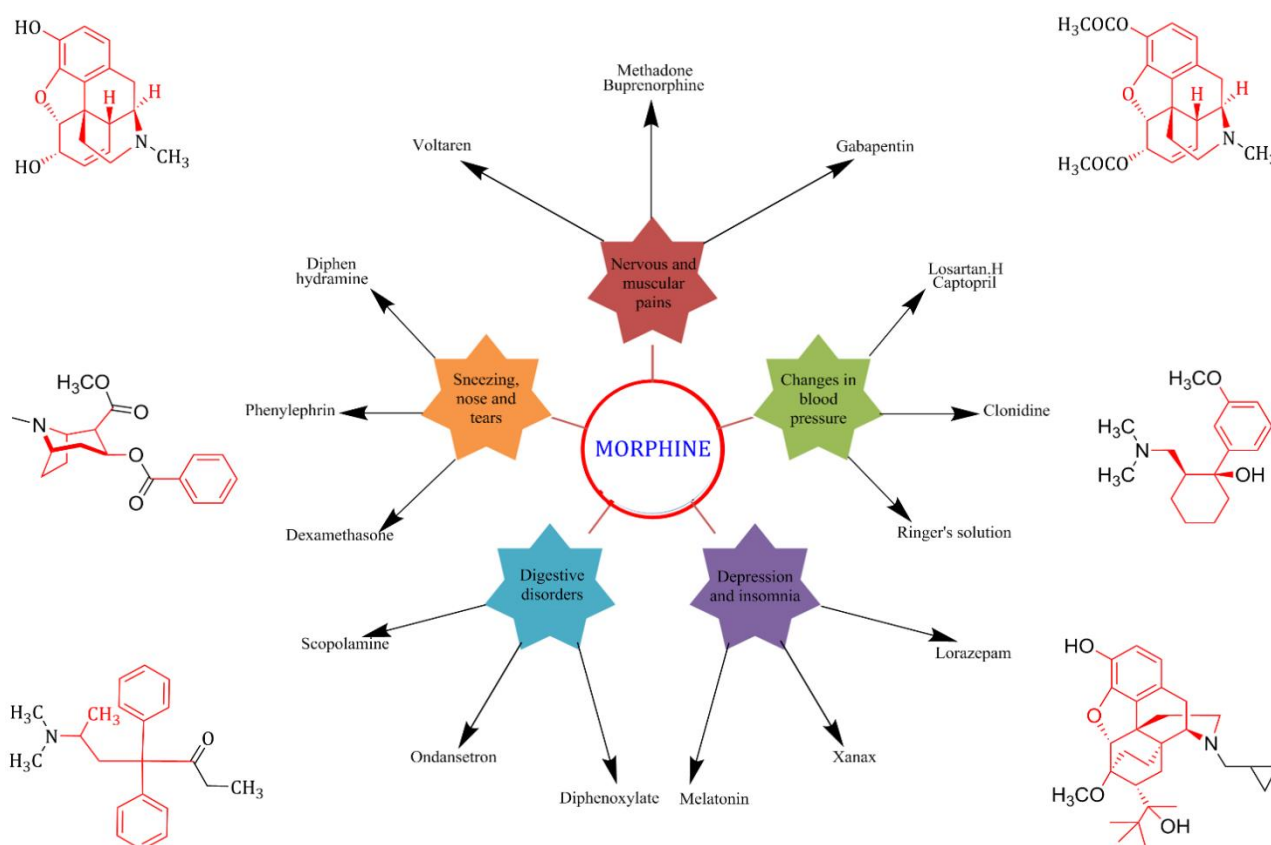
Table 1 The chemical structure of opioids and opioids derived from morphine [8].

 Extraction 				
Nonproprietary Name	Chemical Radicals and Position *			Other Changes ^[†]
	3	6	17	
Morphine	-OH	-OH	-CH ₃	-
Heroin	-OCOCH ₃	-OCOCH ₃	-CH ₃	-
Hydromorphone	-OH	=O	-CH ₃	(1)
Oxymorphone	-OH	=O	-CH ₃	(1), (2)
Levorphanol	-OH	-H	-CH ₃	(1), (3)
Levallorphan	-OH	-H	-CH ₂ CH=CH ₂	(1), (3)
Codeine	-OCH ₃	-OH	-CH ₃	-
Hydrocodone	-OCH ₃	=O	-CH ₃	(1)
Oxycodone	-OCH ₃	=O	-CH ₃	(1), (2)
Nalmefene	-OH	=CH ₂		(1), (2)
Nalorphine	-OH	-OH	-CH ₂ CH=CH ₂	-
Naloxone	-OH	=O	-CH ₂ CH=CH ₂	(1), (2)
Naltrexone	-OH	=O		(1), (2)
Buprenorphine	-OH	-OCH ₃		(1), (4)
Butorphanol	-OH	-H		(1), (2), (3)
Nalbuphine	-OH	-OH		(1), (2)

* According to the line drawing, the morphine molecule is thought to have positions 3, 6, and 17 in it. † Additional alterations in the morphine molecule are as follows: (1) Single instead of double bond within the C7 and C8 (2) OH is included to C14 (3) No oxygen between C4 and C5 (4) Endoetheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7.

Partial opioid agonists such as pentazocine, nalbuphine, buprenorphine, and butorphanol belong to a unique category of opioid medications with distinct characteristics. These drugs bind to opioid receptors in the central nervous system but, unlike full agonists (such as morphine or fentanyl), do not produce the full range of effects. Instead, their effects are partial, which is why they are referred to as partial agonists. This property makes them useful in pain management and the treatment of opioid addiction [8, 9].

Morphine is a well-known flagship agonist that is widely used in cancer treatment. Morphine is one of the derivatives of opium extract, which is obtained from the opium poppy plant [2, 10]. The use of opioids leads to addiction. From a chemical perspective, these substances were referred to as dark classics in chemical neuroscience. Nerve and muscle pains, mental and emotional problems, digestive disorders, sneezing and runny nose and eyes, and blood pressure problems have been mentioned in major articles (Scheme 1) [14-16]. In the following, we will briefly examine these side effects and the chemistry of the drug results reported in each case. The critical point is that this study does not describe the details of clinical methods in the form of methodology and only deals with the chemical structure of effective compounds and drugs related to the amine functional group [17-19].



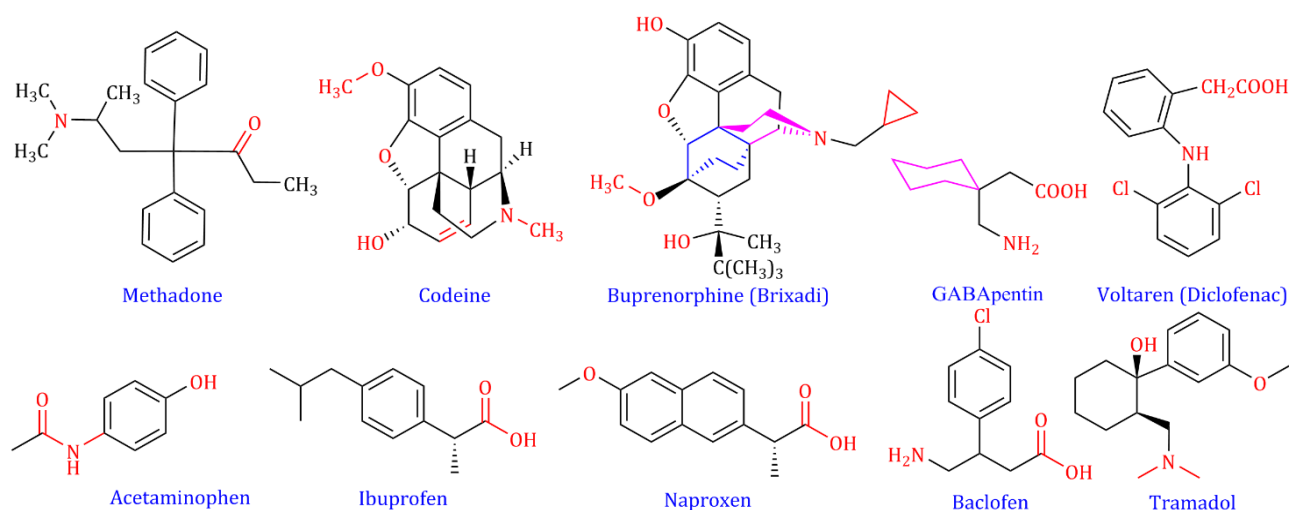
Scheme 1 Morphine and disorders plan.

2. Pain

2.1 Pain Management

Opioids, including opium-derived opiates such as morphine extracted from the poppy plant (Table 1), and the body's natural opioids, prevent pain messages from being sent from chemical synapses to the thalamus by activating mu, alpha, and delta opioid receptors in the body by disrupting the pain message [10, 20]. In essence, by eliminating the sensation of pain, individuals experience a pain-free state due to the repeated use of opium and its derivatives. Over time, this leads to a reduction in the body's natural opioid production, such as endorphins. Simultaneously, the body becomes reliant on the excessive intake of these opioids. Consequently, when the

external source is removed, the body experiences a decline in its pain management capabilities, resulting in the onset of pain and muscle cramps. This discomfort persists until the endocrine glands are stimulated. Engaging in exercise plays a crucial role in facilitating this process, although it requires a relatively short duration to achieve results [8, 21-23]. Research has confirmed that drugs such as methadone [24-26], buprenorphine [21, 27, 28], gabapentin [29], codeine [6, 30], diclofenac (Voltaren) [31], paracetamol [32], ibuprofen [33], baclofen [34], naproxen [35], and methocarbamol are effective in this period to create a feeling of painlessness and muscle cramps depending on the severity of the pain and the treatment timeline [36]. A point to consider in the effect of painkillers or anesthetics is a microbial or viral infection, such as an abscessed tooth. Therefore, antibiotics such as amoxicillin help to eliminate the cause of the disease in parallel with the effectiveness of painkillers [37-42]. Additionally, providing vitamin D (Scheme 2) deficiency treatment is beneficial in the prevention and treatment of drug abuse. Vitamin D plays a crucial role in regulating dopamine, providing neuroprotection, and influencing the response to depression and anxiety, stress, inflammatory effects, immune system regulation, and cognitive function [43]. Except for Voltaren, paracetamol, ibuprofen, baclofen, and naproxen, the other mentioned painkillers with different intensities create drug dependence for the patient. Still, the patient will be able to return to their social life as it was before.



Scheme 2 The chemical structures of painkillers.

2.2 Pain Management Biochemistry

The biochemical process by which opioids inhibit pain signals at chemical synapses involves several key interactions [44]. When morphine and similar opioids attach to their specific receptors, the associated G protein undergoes a conformational change. This G protein interacts with multiple components in the opioid signaling pathway (Figure 1) [44-46]. It enhances the conduction of potassium channels, diminishes the conduction of calcium channels, and suppresses the activity of adenylyl cyclase [8, 9]. Collectively, these alterations decrease the efficacy of the signaling mechanisms responsible for transmitting pain. Presynaptic opioid receptors can modulate neuronal activity by either diminishing excitatory neurotransmission or enhancing inhibitory neurotransmission, while postsynaptic opioid receptors directly inhibit neurotransmission by hyperpolarizing the neurons [45-47].

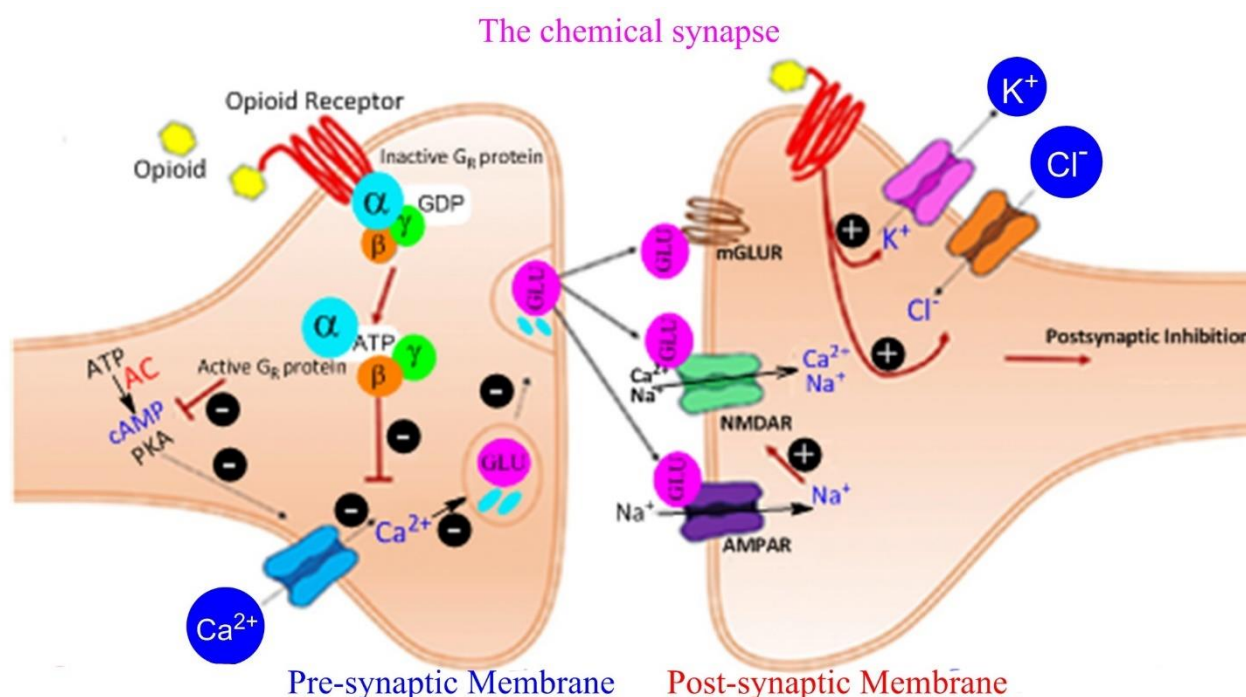


Figure 1 Mechanism of pain management of morphine and opioids in chemical synapses.

3. Mental and Psychological Problems

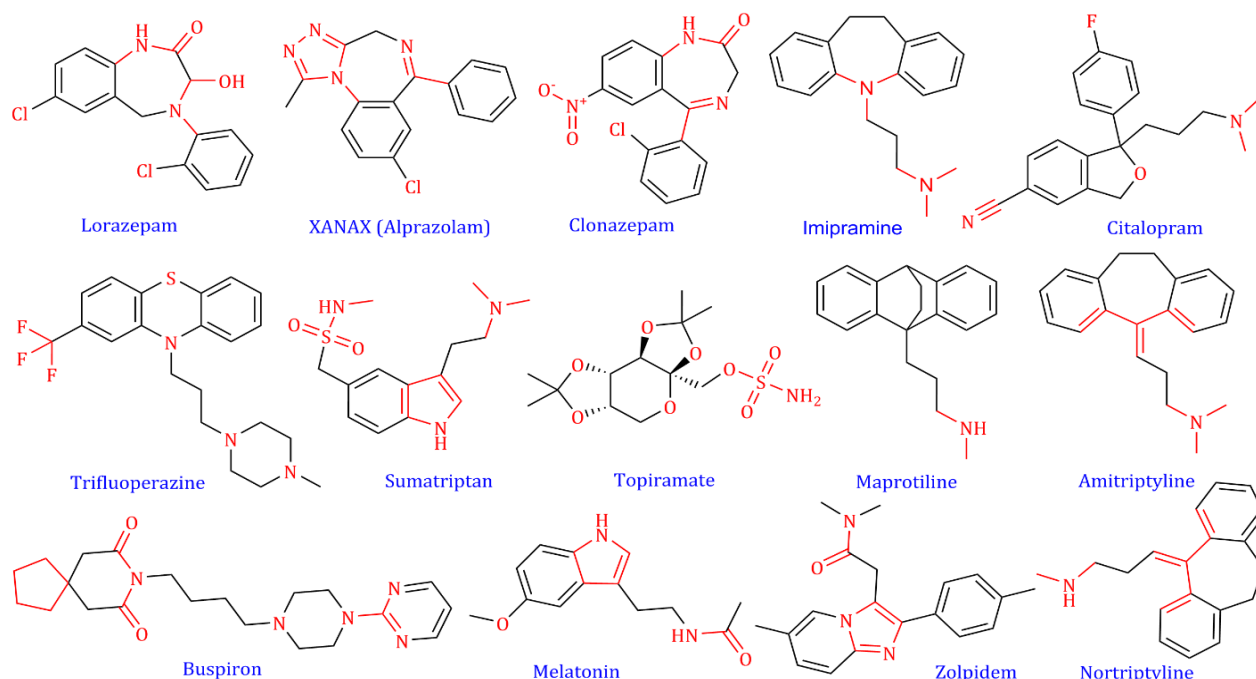
3.1 Mechanism of Mental and Psychological Problems

Opioids by activating opioid receptors in parallel with creating a feeling of painlessness in the thalamus increase the release of gamma amino butyric acid (GABA) and serotonin (5HT) in the nervous system, to reduce shock and stress caused by pain and create relaxation and reduce the feeling of pain [33, 48, 49]. Therefore, over time, the patient becomes psychologically dependent on that external parameter, both in terms of type and quantity, just like the issue of pain. Therefore, by reducing and eliminating this external parameter, the patient suffers from stress, depression, and insomnia [48, 49].

3.2 Management of Mental and Psychological Problems

Research has confirmed that drugs such as lorazepam [50, 51], alprazolam [51, 52], clonazepam [53, 54], imipramine [55-57], amitriptyline [58-60], citalopram [61], trazodone [62], and trifluoperazine [63], are effective by affecting neurotransmitters in this period to create a feeling of relaxation depending on the severity of the mental problem and the treatment timeline. Melatonin [64, 65] and zolpidem [66] are used to improve sleep and regulate the body's sleep time. Melatonin medicine contains melatonin, which is naturally secreted in the body. Melatonin medicine is used to artificially induce the same effects that the hormone creates in the body. Melatonin is a hormone produced by the pineal gland in the brain and plays a vital role in regulating sleep and wakefulness. Zolpidem is an agonist and activator of GABA receptors [66]. Sumatriptan [67], or a combination package of topiramate [68, 69], maprotiline [57, 60, 70], and propranolol [71] is effective for migraine-type nerve pain [41, 72, 73]. Craving for opioids is one of

the side effects of opioid consumption, which is caused by repeated consumption in the body. Buspiron is effective in such cases (Scheme 3) [51, 74, 75].



Scheme 3 The chemical structures of antidepressant drugs.

4. Digestive Disorders

4.1 Biochemistry of Digestive Disorders

Gastrointestinal disorders during the process of addiction withdrawal (such as withdrawal from opioids, alcohol, or other substances) result from complex changes in the nervous and hormonal systems of the body. These changes impact the gastrointestinal system's functioning, resulting in symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite. Below, the biochemical pathways associated with these disorders are explained [76-80]:

4.1.1 Dysfunction of the Endogenous Opioid System

Drugs (such as morphine and heroin) bind to opioid receptors (μ , δ , κ) in the gastrointestinal tract and central nervous system, regulating the normal functioning of the digestive system. During withdrawal, the sudden decrease in the activity of these receptors leads to disruptions in bowel movements (increased bowel movements and diarrhea) and reduced secretion of digestive enzymes [76-80].

4.1.2 Changes in the Dopaminergic System

Dopamine is an important neurotransmitter in regulating bowel movements and the sensation of nausea. During withdrawal, a decrease in dopamine levels in the brain's reward system and gastrointestinal tract leads to increased nausea and vomiting [76-81].

4.1.3 Increased Activity of the Noradrenergic System

During withdrawal, the activity of the noradrenergic system (norepinephrine) significantly increases. This overstimulation affects the gastrointestinal system, causing symptoms such as abdominal pain, diarrhea, and loss of appetite [76-78, 80].

4.1.4 Changes in the Serotonergic System

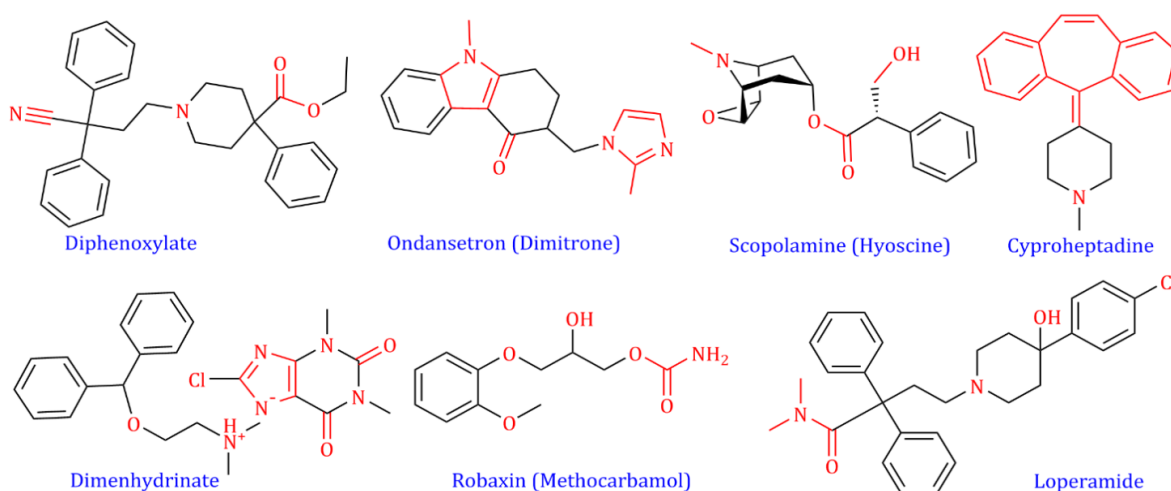
Serotonin (5-HT) plays a key role in regulating bowel movements and the sensation of nausea. During withdrawal, changes in serotonin levels can lead to increased bowel movements (diarrhea) and stimulation of the brain's nausea center. During alcohol withdrawal, reduced activity of the GABAergic system (gamma-aminobutyric acid) and increased glutamatergic activity lead to overstimulation of the nervous and gastrointestinal systems. These changes result in nausea, vomiting, and abdominal pain [76-80].

4.1.5 Inflammation and Oxidative Stress

Withdrawal from addiction increases levels of inflammation and oxidative stress in the body. These factors can damage gastrointestinal cells, leading to symptoms such as abdominal pain and impaired digestion [76-80].

4.2 Management of Digestive Disorders

The most common digestive disorders in the period of the first line (first days) of quitting an addiction, abdominal pains, diarrhea, nausea, and vomiting, can appear with different intensity depending on the conditions of the people and the chosen path of treatment and therapeutic drugs [82-84]. Research has confirmed that drugs such as diphenoxylate [82, 83], loperamide [84], in the treatment of diarrhea, hyoscine [85-87], and methocarbamol for abdominal cramps, ondansetron [88], and dimenhydrinate [89], for nausea and vomiting are effective in this period to help the patient and endure the effects of addiction withdrawal. Cyproheptadine is effective for the treatment of anorexia [90], and in parallel, for the prevention of migraine with the origin of an empty stomach, as well as the treatment of allergic complications (Scheme 4) [81, 90].



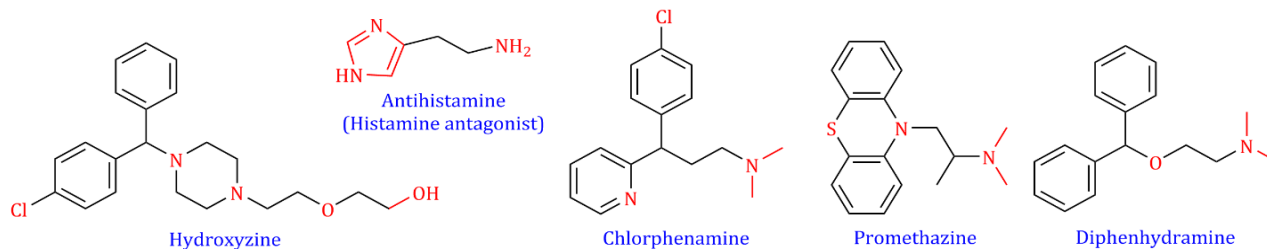
Scheme 4 The chemical structures of gastrointestinal drugs.

5. Sneezing and Runny Nose, and Eyes

5.1 Managing the Effects of the Sympathetic and Parasympathetic Systems

Rhinorrhea (runny nose) is a prevalent symptom. It is often caused by allergies and viral infections (such as a cold or flu). However, several other diseases can cause your runny nose. A runny nose usually clears up on its own over time, but specific treatments can help alleviate it. Stimulation of the parasympathetic nervous system (PSNS) leads to increased mucus production and release [91-93]. Histamine (the chemical that causes allergic reactions) stimulates the permeability of blood vessels and the dilation of blood vessels, resulting in a runny nose [92, 93]. The autonomic nervous system (sympathetic and parasympathetic) controls the body's automatic functions such as blood circulation, digestion, breathing, urination, and heart rate. For this reason, this system is called automatic, because without a person making a conscious effort, these things are done automatically in his body by this system [91-93]. The sympathetic system is a part of the autonomic nervous system that is located near the thoracic and lumbar regions of the spinal cord. The primary function of this system is to stimulate the fight or flight system in the human body, which does this by regulating heart rate, breathing rate, and pupil size. This system prepares the body to react to stress or emergencies. Factors such as excitement, anxiety, fear, pain, and cold stimulate this system, causing rapid physical reactions in the body [91-94]. The parasympathetic autonomic nervous system is located between the spinal cord and medulla and controls rest, digestion, and reproductive reactions. In general, the sympathetic nervous system prepares the body for a fight or flight response in situations where there is a possibility of danger. On the other hand, the parasympathetic nervous system prevents excessive body activity and puts the body in a state of rest [92, 93]. The difference between these two systems is in the body's reaction to environmental stimuli. When the body is in a stressful situation, the amygdala, which is the emotional processing center in the brain, sends a stress signal to the hypothalamus [92, 93]. The hypothalamus acts as a command center, communicating with the body through the nervous system. When the amygdala sends a stress signal to the hypothalamus, the hypothalamus activates the sympathetic nervous system. The sympathetic system, in turn, stimulates the adrenal glands and causes the release of epinephrine or adrenaline in the body [92, 93]. Adrenaline increases the heart rate and blood supply to the muscles and increases the breathing rate so that enough oxygen reaches the organs of the body. When a patient experiences situations of fear or stress, the hypothalamus activates the parasympathetic nervous system. It releases the hormone acetylcholine, which slows down the heartbeat and breathing and returns the body to a state of relaxation [92, 93]. The parasympathetic nervous system plays a crucial role in safeguarding and repairing the body's organs. It functions by lowering heart rate and blood pressure, decreasing the breathing rate, facilitating digestion, and promoting a relaxed state within the digestive system. When opioids are used, this system becomes stimulated, leading to a continuous release of the hormone acetylcholine, which further induces relaxation throughout the body [92, 93]. By removing or reducing the number of opioids in the body, the parasympathetic system is shocked, in other words, the body is faced with a small amount of acetylcholine hormone. Therefore, the sympathetic system is automatically activated under shock, and the release of histamine and adrenaline increases. Runny nose, tears, and sneezing begin in an allergic way [92, 93]. Research has confirmed that drugs such as antihistamine [95, 96], chlorpheniramine [97], diphenhydramine

[14, 89], promethazine [29], hydroxyzine [51, 98, 99], and dexamethasone [100], are effective in this period in eliminating these side effects in the first line of treatment (Scheme 5).



Scheme 5 The chemical structures of anti-allergic drugs.

5.2 Biochemistry of Sneezing and Runny Nose, and Eyes

Runny nose, watery eyes, and sneezing are common symptoms during addiction withdrawal, particularly in opioid withdrawal (such as from heroin or morphine). These symptoms are part of the Opioid Withdrawal Syndrome and result from biochemical changes in the nervous system and the release of certain neurotransmitters and hormones. Below, the biochemical pathways associated with these symptoms are explained [77, 80, 81, 101]:

5.2.1 Increased Activity of the Noradrenergic System (Norepinephrine)

During opioid withdrawal, the activity of the noradrenergic system significantly increases. This increase is due to the reduced inhibition of opioid receptors on noradrenergic neurons in the Locus Coeruleus in the brain. Excessive norepinephrine stimulates the tear and nasal glands, leading to watery eyes and a runny nose. Additionally, this increased activity can stimulate sensory nerves in the nose, causing sneezing [78, 80, 102].

5.2.2 Dysfunction of the Endogenous Opioid System

External opioids (such as morphine) bind to opioid receptors (μ , δ , κ) in the body, disrupting the normal functioning of the endogenous opioid system. During withdrawal, reduced activity of these receptors leads to increased activity of excitatory nervous systems (such as the noradrenergic system), causing symptoms like a runny nose and watery eyes [80, 102].

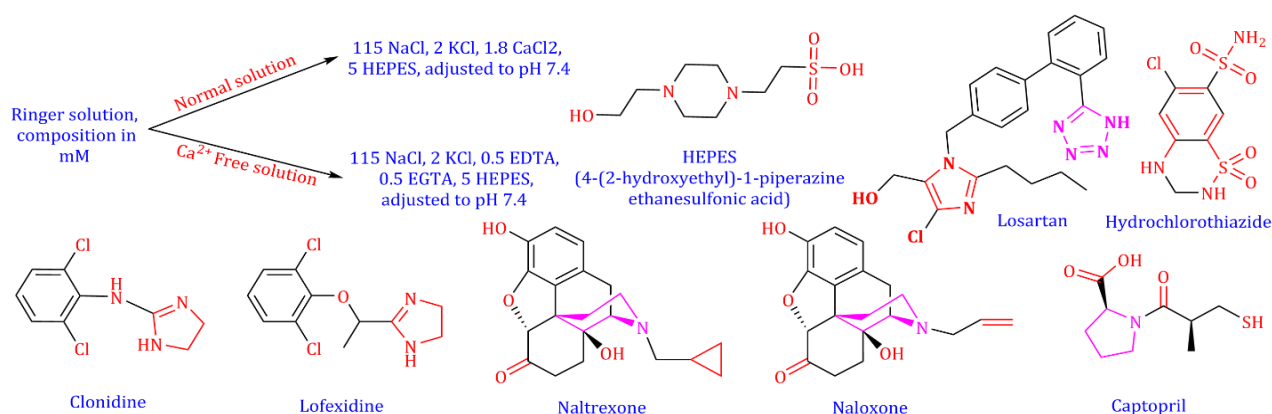
5.2.3 Changes in the Histaminergic System

During withdrawal, increased activity of the noradrenergic system can trigger the release of histamine from mast cells. Histamine is a potent inflammatory mediator that causes vasodilation, increased mucus secretion, and stimulation of sensory nerves. This process leads to a runny nose, watery eyes, and sneezing. The cholinergic system also plays a role in regulating secretions from glands (such as the tear and nasal glands). During withdrawal, increased cholinergic activity can lead to excessive secretions from these glands [80, 102].

6. Changes in Blood Pressure

6.1 Manage Blood Pressure Changes

During the initial period of treatment, digestive problems can cause the body to lose fluid and electrolytes, resulting in a reduction in blood pressure. Therefore, during this period, the patient is administered Ringer's solution, which contains the appropriate electrolytes and aids in the process of poisoning. It is suitable for the auscultation of the body. According to research, clonidine [103] and lofexidine [104-107] are used in cases of high blood pressure. Clonidine is a drug that is used to treat high blood pressure, attention deficit hyperactivity disorder, drug withdrawal (alcohol, opioids, or opiates), menopausal hot flashes, diarrhea, and in some specific conditions, pain [103, 108-110]. Clonidine is one of the drugs that reduce blood pressure and anxiety. Tricyclic antidepressants may reduce the blood pressure-lowering effects of clonidine. If clonidine is used simultaneously with beta-adrenergic receptor blockers, discontinuation of clonidine may cause a blood pressure crisis and stress [103]. Lofexidine is approved for a treatment duration of 14 days in the United States to reduce withdrawal symptoms and facilitate abrupt withdrawal of opioids in adults. In the UK, lofexidine is commonly used in combination with the opioid receptor antagonist, naltrexone, in rapid detoxification [105, 111, 112]. When these two drugs are paired together, naltrexone is administered to block the opioid receptor, leading the subject to immediate withdrawal and speeding up the detoxification process. Lofexidine is also prescribed to relieve symptoms related to withdrawal, such as chills, sweating, stomach cramps, and muscle cramps. One of the proposed uses for lofexidine is to alleviate methadone withdrawal symptoms. This drug is an α_2A adrenergic receptor agonist. It was approved by the US Food and Drug Administration in 2018 [105]. Naloxone and naltrexone are among the antagonist drugs that are used in cases of rapid detoxification or cases of opioid overdose [113]. Losartan [114], losartan-H (losartan-hydrochlorothiazide) [115], and captopril [116] are used to treat hypertension or high blood pressure to prevent the feeling of suffocation and respiratory retention. UK National Institute for Health and Care Excellence (NICE) guidelines recommend the use of methadone or buprenorphine as first-line agents in the management of opioid use disorder. However, lofexidine is considered an acceptable alternative for people with mild or undiagnosed opioid dependence who require short-term detoxification. Lofexidine is not an opioid. It does not reverse opioid withdrawal symptoms, but it reduces them (Scheme 6) [104].



Scheme 6 The chemical structures of Blood Pressure and Detoxification.

6.2 Biochemistry of Opioid-Induced Blood Pressure Changes

Opioid withdrawal can lead to significant changes in blood pressure. These changes result from the overactivation of neural and hormonal systems that were previously suppressed by opioids. Below are the biochemical mechanisms of these changes [117-123]:

6.2.1 Overactivation of the Sympathetic Nervous System

During opioid withdrawal, the activity of the sympathetic nervous system significantly increases. This heightened activity leads to excessive secretion of catecholamines (such as epinephrine and norepinephrine), which cause an increase in heart rate and vasoconstriction, resulting in elevated blood pressure [117-119].

6.2.2 Changes in the Renin-Angiotensin-Aldosterone System (RAAS)

Opioid withdrawal can activate the RAAS. Increased levels of renin and angiotensin II cause vasoconstriction and elevated blood pressure. Additionally, increased aldosterone levels lead to sodium and water retention, increasing blood volume and blood pressure [117-119].

6.2.3 Changes in Hormone Secretion

Opioid withdrawal can alter the secretion of hormones such as cortisol and vasopressin. Increased cortisol levels raise blood pressure by enhancing vascular sensitivity to catecholamines. Vasopressin also increases blood pressure by promoting water retention and vasoconstriction [117-119].

6.2.4 Reduced Activity of the Parasympathetic Nervous System

During opioid withdrawal, the activity of the parasympathetic nervous system decreases. This reduction leads to increased heart rate and reduced vasodilation, both of which contribute to elevated blood pressure [117-119].

6.2.5 Changes in Nitric Oxide (NO) Levels

Opioid withdrawal can reduce the production of nitric oxide (NO). NO is a key factor in vasodilation, and its decreased levels can cause vasoconstriction and increased blood pressure [117-119, 122].

6.2.6 Changes in the Endocannabinoid System

Some studies suggest that opioid withdrawal may involve changes in the endocannabinoid system, which also plays a role in blood pressure regulation. Overactivation of this system can lead to increased blood pressure [117-119, 124].

7. Traditional Medicine in the Treatment of Drug Abuse

Herbal remedies have gained attention as a complementary approach in the treatment of addiction (Figure 2, Figure 3, and Figure 4). Some medicinal plants that may be effective in overcoming addiction include [125-127]:

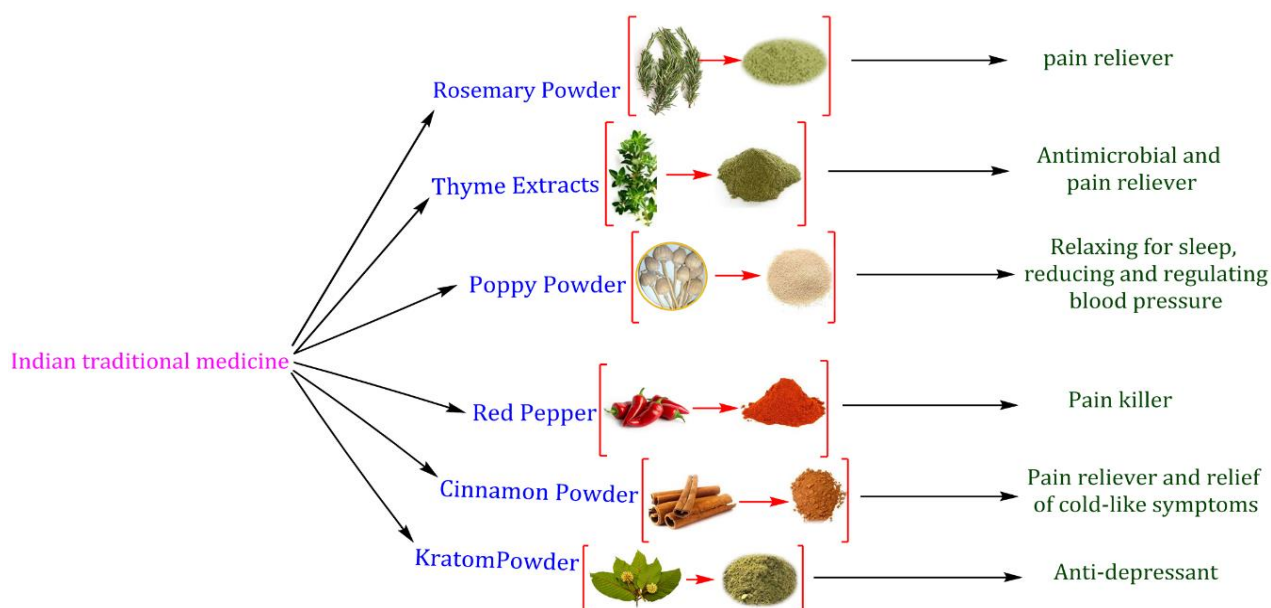


Figure 2 Indian herbal medicine for addiction treatment known as Indian Deta or Dragon Medicine.



Figure 3 The chemical structure of harmaline.

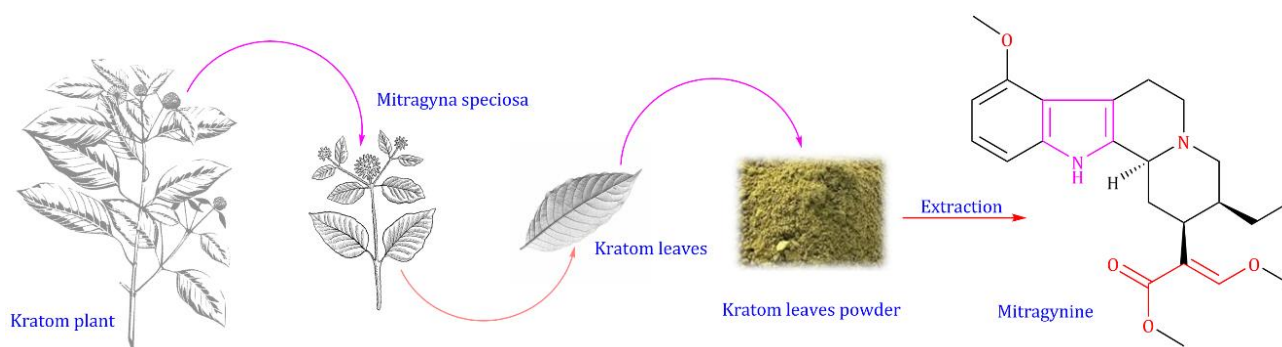


Figure 4 The chemical structure of mitragynine.

7.1 Passionflower (*Passiflora Incarnata*)

Reduces anxiety and insomnia, which commonly occur during the withdrawal process: Studies have shown that passionflower can help alleviate anxiety symptoms and improve sleep [125].

7.2 Valerian (*Valeriana Officinalis*)

Reduces anxiety and improves sleep: Research indicates that valerian can help reduce anxiety symptoms and enhance the quality of sleep [126].

7.3 Turmeric (*Curcuma Longa*)

Reduces inflammation and oxidative stress, which may play a role in the addiction withdrawal process. Studies have shown that curcumin, the active compound in turmeric, can help reduce inflammation and oxidative stress [127].

7.4 Ginseng (*Panax Ginseng*)

Improves cognitive function and reduces fatigue: Research suggests that ginseng can help enhance mental function and reduce fatigue [128].

7.5 Peppermint (*Mentha Piperita*)

Reduces nausea and vomiting, which may occur during the withdrawal process. Studies have shown that peppermint can help alleviate nausea and vomiting [129].

7.6 Chamomile (*Matricaria Chamomilla*)

Reduces anxiety and improves sleep: Research indicates that chamomile can help alleviate anxiety symptoms and promote better sleep [130].

7.7 Rosemary (*Rosmarinus Officinalis*)

Improves cognitive function and reduces stress: Studies have shown that rosemary can help enhance mental function and reduce stress [131].

7.8 Saffron (*Crocus Sativus*)

Reduces symptoms of depression and anxiety: Research suggests that saffron can help alleviate symptoms of depression and anxiety [132].

7.9 Green Tea (*Camellia Sinensis*)

Reduces stress and improves cognitive function: Research indicates that green tea can help reduce stress and enhance mental function [133].

7.10 Harmaline

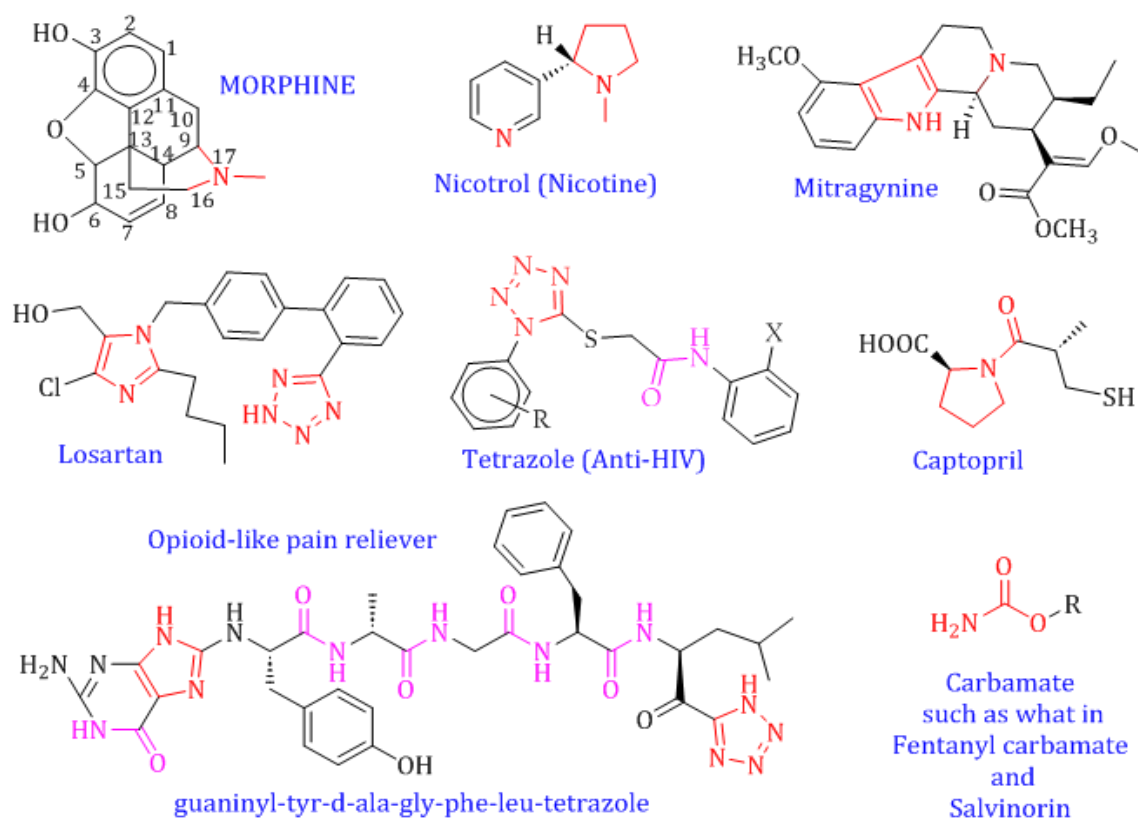
Harmaline is an alkaloid compound found in plants such as *Peganum harmala* (Syrian rue). This compound has been studied for its psychoactive and medicinal properties. Harmaline is known as a monoamine oxidase inhibitor (MAOI) and may be effective in treating certain psychiatric disorders and addiction. However, research on the effects of harmaline on addiction recovery is limited [134-136]. Since the flag bearer of opioids has an herbal aspect, it is not irrelevant if we say that the least dangerous in terms of side effects in the treatment of drug abuse can be herbal [2]. Among the medicinal plants, the black seeds of the pecan plant have the potential to be used in treatment due to the presence of a substance called harmaline (Figure 3) [87].

7.11 Kratom

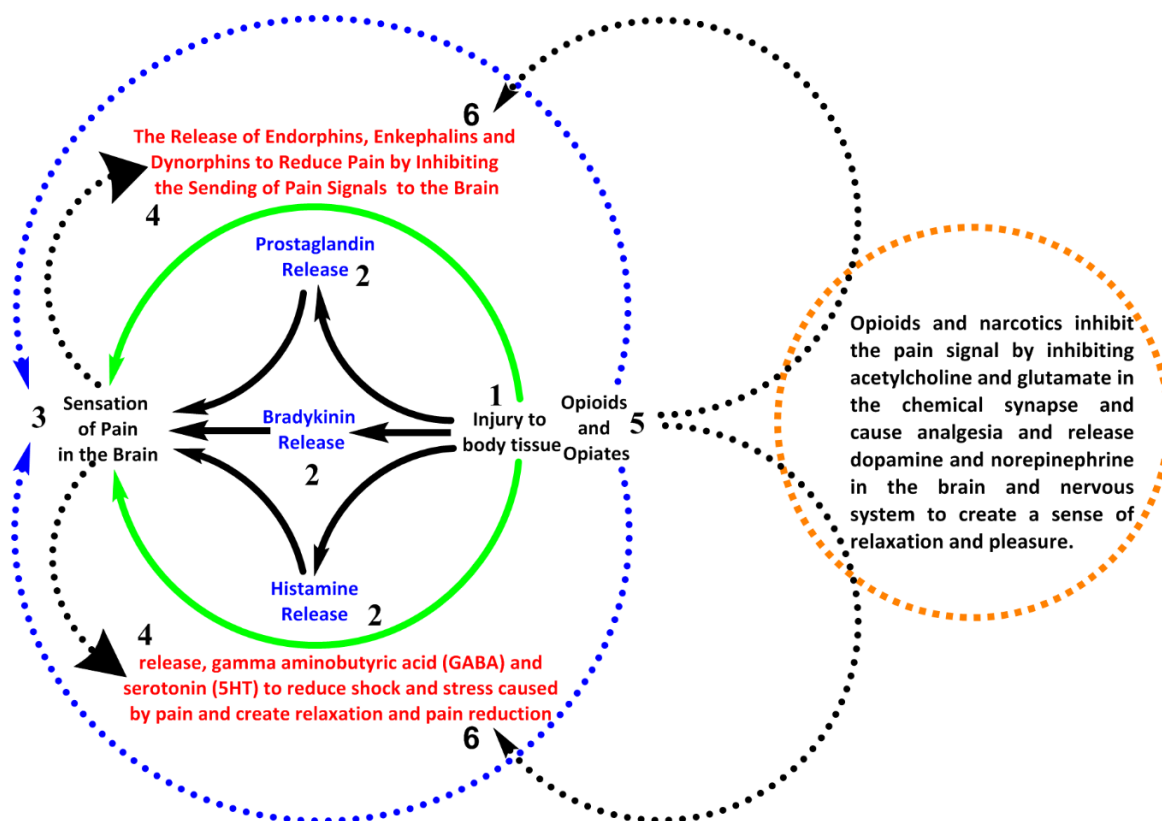
Kratom is a plant native to Southeast Asia and has gained attention for its medicinal properties. Some studies and reports suggest that kratom may be beneficial in overcoming addiction to drugs, particularly opioids such as heroin and morphine. This plant contains compounds like mitragynine and 7-hydroxy mitragynine (Figure 4), which act on opioid receptors in the brain and may help alleviate withdrawal symptoms and reduce cravings for addictive substances [9, 137-140].

8. The Medicinal Effect of the Chemical Structure of N-Heterocyclic Amines

As it can be concluded from the structures, most of the used drugs have N-heterocyclic or N-amine resonance structures [8, 141, 142]. This group of chemical compounds is of special importance in chemical and biochemical sciences, as well as in pharmaceuticals, due to their numerous biological and biochemical applications, on the one hand, and their complex synthesis, on the other hand [143-148]. The medicinal significance of 5- and 6-membered n-amine rings has been widely acknowledged and documented within the pharmaceutical sector [149-151]. The role of amines in both chemistry and pharmaceutical science is crucial, primarily due to their biological properties, which are found in compounds such as amino acids, glucosamine, adrenaline, dopamine, endorphins, and urea. Tautomeric character, which is a key aspect in chemistry, is influenced by the resonance of heteroatoms. Recent research has demonstrated the presence of this valuable chemical characteristic in derivatives of tetrazole, pyrrole, piperidine, and carbamates, underscoring its relevance in medicinal neurochemistry (Scheme 7). Chemical synapses serve as the sites for the exchange and transmission of nerve signals, with chemical nerve agents acting on receptors within the synaptic space. These synapses are situated in the central nervous system (CNS), which is encased in lipid and fatty tissues. For drugs to effectively target the synaptic space, they must possess the ability to penetrate the CNS, which includes traversing fatty tissues and crossing the blood-brain barrier. The biological significance of amine derivatives is highlighted by their solubility in fatty tissues and their capacity to cross the blood-brain barrier. Morphine stands out as a leading opioid and one of the most significant chemical nerve agents, recognized for its potent analgesic and sedative effects (Scheme 8) [8, 9].



Scheme 7 Synthesized N-heterocycles and amines with morphine-like and opioid properties.



Scheme 8 Pharmacological action and neurobiology of morphine and opioid-like.

8.1 Reasons for the Use of Heterocycles in Nervous System Drugs

Heterocycles play a significant role in the design of nervous system drugs due to their unique structural and chemical properties. These compounds are widely used in the treatment of neurological and psychiatric disorders. Below, the main reasons for their application are explained [92, 152, 153].

8.1.1 Structural Features of Heterocycles

Structural Diversity. Heterocycles are ring structures that contain non-carbon atoms (such as nitrogen, oxygen, or sulfur). This structural diversity allows for the design of molecules with diverse pharmacological properties [154, 155].

Chemical Stability. Heterocyclic rings are generally stable and can withstand physiological conditions in the body [156].

Receptor Binding Capability. The presence of heteroatoms (such as nitrogen) enables these compounds to easily interact with receptors, enzymes, and other biological molecules in the nervous system [93].

8.1.2 Reasons for the Use of Heterocycles in Nervous System Drugs

Similar to Neurotransmitters. Many heterocycles have structures identical to neurotransmitters (e.g., dopamine, serotonin, GABA, and acetylcholine). This similarity allows them to act as agonists or antagonists of these receptors.

For example, Benzodiazepines (e.g., diazepam), which contain heterocyclic rings, exert calming and anti-anxiety effects by binding to GABA-A receptors [92].

Ability to Cross the Blood-Brain Barrier (BBB). Heterocycles often possess lipophilic (fat-soluble) properties, enabling them to cross the blood-brain barrier and reach the central nervous system. For example, Tricyclic antidepressants (e.g., amitriptyline), which contain heterocyclic rings, readily penetrate the brain [93].

Diverse Pharmacological Activity. Heterocycles can act on various receptors, enzymes, and ion channels in the nervous system. This versatility makes them helpful in treating a wide range of neurological disorders. For example, Antipsychotic drugs (e.g., olanzapine), which contain heterocyclic rings, target dopamine and serotonin receptors [92, 153].

8.1.3 Advantages of Heterocycles in Designing Nervous System Drugs [92, 93, 153]

Flexibility. Enables the design of new drugs with improved properties.

Precise Targeting. Allows targeting of specific receptors or enzymes in the nervous system.

Reduced Side Effects. Facilitates the design of drugs with fewer side effects compared to non-heterocyclic compounds.

8.2 The Relevance of Findings from Various Studies on the Use of Heterocycles and Amines in Chemical Neuroscience

Findings from various studies in the field of chemical neuroscience indicate that heterocyclic compounds and amines play a significant role in regulating nervous system function, treating neurological and psychiatric disorders, and developing novel drugs. Due to their unique chemical structures and ability to interact with receptors, neurotransmitters, and enzymes associated with the nervous system, these compounds have garnered widespread attention [157]. Below are some key applications and findings from studies on these compounds:

8.2.1 Heterocyclic Compounds in Neuroscience

Heterocyclic compounds (rings containing non-carbon atoms such as nitrogen, oxygen, or sulfur) have diverse structural and biological activities, making them highly valuable in neuroscience [157]. Some key findings include:

Regulation of Neurotransmitters. Heterocyclic compounds such as benzodiazepines (e.g., diazepam) bind to GABA-A receptors, producing sedative and anxiolytic effects. These compounds are used to treat anxiety disorders and seizures. Pyridines and pyrimidines also play a role in designing drugs that target the dopaminergic and serotonergic systems. For example, olanzapine (an antipsychotic) contains heterocyclic rings and is used to treat schizophrenia and bipolar disorder [92].

Inhibition of Enzymes Associated with Neurological Disorders. Heterocyclic compounds such as donepezil (an acetylcholinesterase inhibitor) are used to treat Alzheimer's disease. These drugs increase acetylcholine levels in the brain by inhibiting the enzyme that breaks it down. Rosuvastatin (containing a pyrrole ring), a cholesterol-lowering drug, is effective in preventing stroke and cerebrovascular diseases [73, 92, 93].

Antioxidant and Neuroprotective Activity. Some heterocyclic compounds, such as melatonin (containing an indole ring), have antioxidant properties and protect neurons from oxidative stress [92, 93, 153].

8.2.2 Amines in Neuroscience

Amines. Amines (compounds containing the amino group $-NH_2$) [158, 159] are crucial in neuroscience due to their role in the structure of neurotransmitters and receptors [93]. Some key findings include:

(i) Neurotransmitters. Dopamine, serotonin, and norepinephrine are among the most crucial amine neurotransmitters involved in regulating mood, behavior, and cognitive function. Dysregulation of these systems is associated with disorders such as depression, anxiety, and Parkinson's disease. Antidepressants like fluoxetine (a serotonin reuptake inhibitor) and bupropion (a norepinephrine and dopamine reuptake inhibitor) alleviate symptoms of psychiatric disorders by modulating the amine system [92, 93, 153].

(ii) Adrenergic and Dopaminergic Receptors. Amine compounds such as propranolol (a beta-blocker) bind to adrenergic receptors and are used to treat anxiety and hypertension. Levodopa (a dopamine precursor) is used to treat Parkinson's disease by crossing the blood-brain barrier and increasing dopamine levels in the brain [93].

(iii) Inhibition of Amine-Related Enzymes. Monoamine oxidase inhibitors (MAOIs), such as selegiline, increase neurotransmitter levels in the brain by inhibiting the enzymes that break down amines and are used to treat depression and Parkinson's disease [93].

8.3 Combining Heterocycles and Amines in Drug Design

The combination of heterocyclic and amine structures in drug design enables the development of compounds with enhanced biological activity [152, 157]. For example:

8.3.1 Risperidone

Risperidone (an antipsychotic) contains both heterocyclic and amine groups and is used to treat schizophrenia and psychiatric disorders.

8.3.2 Donepezil

Donepezil (containing an indole ring and an amine group) is effective in treating Alzheimer's disease.

9. Opioid Withdrawal Side Effects and Treatment: Classification and Details

Opioid withdrawal can be highly uncomfortable and, in some cases, medically challenging. Treatment focuses on managing symptoms, preventing complications, and supporting long-term recovery [160-168]. Below is a detailed classification of opioid withdrawal side effects and their treatment options, along with references to clinical guidelines [15, 160].

9.1 Classification of Opioid Withdrawal Side Effects

Opioid withdrawal symptoms are categorized into early and late stages, based on the timeline of onset and progression [15].

9.1.1 Early Symptoms (6-12 Hours after Last Dose) [169, 170]

Physical Symptoms.

- (a) Muscle Aches
- (b) Agitation
- (c) Sweating
- (d) Runny nose
- (e) Yawning
- (f) Tearing (Lacrimation)

Psychological Symptoms.

- (a) Anxiety
- (b) Restlessness
- (c) Insomnia

9.1.2 Late Symptoms (24-72 Hours after Last Dose) [169, 170]

Physical Symptoms.

- (a) Nausea
- (b) Vomiting
- (c) Diarrhea
- (d) Abdominal cramps
- (e) Dilated pupils (mydriasis)
- (f) Goosebumps (piloerection)
- (g) Rapid heartbeat (tachycardia)
- (h) High blood pressure (hypertension)

Psychological Symptoms.

- (a) Depression
- (b) Intense cravings
- (c) Irritability

9.1.3 Timeline [169, 170]

Short-Acting Opioids (e.g., Heroin, Oxycodone). Symptoms begin within 6-12 hours, peak at 1-3 days, and subside within 5-7 days.

Long-Acting Opioids (e.g., Methadone). Symptoms begin within 24-48 hours, peak at 3-5 days, and may last 1-2 weeks.

9.2 Treatment of Opioid Withdrawal

Treatment strategies aim to alleviate symptoms, reduce cravings, and prevent relapse. They are classified into pharmacological and non-pharmacological approaches.

9.2.1 Pharmacological Treatments [169, 170]

Opioid Agonist Therapy (OAT).

(i) Methadone. A long-acting opioid agonist that reduces withdrawal symptoms and cravings. Administered in controlled, tapering doses under medical supervision. Dosage: Typically starts at 20-30 mg/day, adjusted based on response.

(ii) Buprenorphine. A partial opioid agonist that alleviates withdrawal symptoms with a lower risk of misuse. Often combined with naloxone (Suboxone) to deter misuse. Dosage: Initial dose of 2-4 mg, titrated to 8-16 mg/day.

Alpha-2 Adrenergic Agonists.

(i) Clonidine. Reduces sympathetic nervous system hyperactivity (e.g., sweating, tachycardia, hypertension). Dosage: 0.1-0.3 mg every 4-6 hours, as needed.

(ii) Lofexidine. Similar to clonidine but with fewer side effects (e.g., less hypotension). Explicitly approved for opioid withdrawal. Dosage: 0.54 mg every 6-8 hours, up to 2.16 mg/day.

Symptomatic Relief Medications.

(i) Anti-Diarrheals. Loperamide for Diarrhea.

(ii) Anti-Emetics. Ondansetron or Metoclopramide for Nausea and Vomiting.

(iii) NSAIDs. Ibuprofen or acetaminophen for muscle aches and pain.

(iv) Benzodiazepines. Short-term use for anxiety and insomnia (used cautiously due to addiction risk).

(v) Naltrexone. An opioid antagonist is used after detoxification to prevent relapse. Oral: 25 mg initially, increasing to 50 mg/day. Injectable (Vivitrol): 380 mg monthly.

9.2.2 Non-Pharmacological Treatments

Behavioral Therapies.

(i) Cognitive Behavioral Therapy (CBT). Helps patients identify and change negative thought patterns and behaviors.

(ii) Contingency Management. Provides incentives for positive behaviors (e.g., drug-free urine tests).

(iii) Motivational Interviewing. Enhances motivation to stay sober.

Support Groups.

(i) 12-Step Programs. Narcotics Anonymous (NA) and similar groups provide peer support.

(ii) Counseling. Individual or group therapy to address underlying issues.

Medical Monitoring.

(i) Inpatient or Outpatient Detox Programs to Ensure Safety and Provide Support.

9.3 Clinical Guidelines

9.3.1 World Health Organization (WHO)

Guidelines for the management of opioid dependence recommend opioid agonist therapy (e.g., methadone, buprenorphine) as the first-line treatment.

9.3.2 American Society of Addiction Medicine (ASAM)

Recommends a combination of pharmacological and behavioral therapies for opioid withdrawal and long-term recovery.

9.3.3 National Institute on Drug Abuse (NIDA)

Highlights the importance of medication-assisted treatment (MAT) for opioid use disorder.

9.4 Key Considerations

9.4.1 Individualized Treatment

Tailor treatment to the patient's needs, including co-occurring mental health disorders.

9.4.2 Relapse Prevention

Long-term management with naltrexone or ongoing therapy is crucial.

9.4.3 Medical Supervision

Severe withdrawal should be managed in a medical setting to prevent complications [160-170].

10. Conclusions

The review highlights the intricate relationship between chemical structures and their pharmacological effects, particularly focusing on heterocyclic N-amine drugs and their implications in managing pain, mental health, and addiction. The findings emphasize that opioids, while effective for pain relief, can lead to significant psychological dependence and withdrawal symptoms. These necessitate comprehensive treatment strategies that include both pharmacological and non-pharmacological approaches. The biochemical mechanisms underlying opioid action reveal that these substances inhibit pain signals by interacting with specific receptors, which can lead to alterations in neurotransmitter systems, contributing to both therapeutic effects and adverse outcomes. The review discusses the potential of traditional medicine, including various herbal remedies, as adjuncts in addiction treatment, suggesting that these natural compounds may offer benefits with fewer side effects compared to synthetic drugs. The structural diversity and receptor-binding capabilities of heterocycles are highlighted as critical factors in drug design, enabling precise targeting and reduced side effects. Overall, the review underscores the importance of understanding the biochemical pathways involved in drug action and withdrawal to develop effective treatment protocols for opioid dependence and related disorders, advocating for a multidisciplinary approach to address the complexities of addiction and pain management.

Acknowledgments

This research was supported by the Zabol University, Sistan and Baluchestan University, and Zahedan University of Medical Science.

Author Contributions

Prof. Dr. Ferydoon Khamooshi: Research admin, Data analysis and Editor. Samaneh Doraji-Bonjar Clinical Specialist: Data collection and author. Prof. Dr. Habib Ghaznavi: Scientific advisor. Prof. Dr. Mohammad Hasan Mohammadi: Scientific advisor. Prof. Dr. Ali Reza Modarresi-Alam: Scientific advisor. Prof. Dr. Ali Navidian: Scientific advisor. Prof. Dr. Ali Khajeh: Scientific advisor. Prof. Dr. Mohammad Kazem Momeni: Scientific advisor.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Fernández Velázquez J, Smith B. A history of opium commodity chains in Mexico, 1900–1950. *J Illicit Econ Dev*. 2022; 4: 113-127.
2. Ekhtiari H, Noroozi A, Farhoudian A, Radfar SR, Hajebi A, Sefatian S, et al. The evolution of addiction treatment and harm reduction programs in Iran: A chaotic response or a synergistic diversity? *Addiction*. 2020; 115: 1395-1403.
3. Al-Worafi YM. Drug abuse in developing countries. In: *Handbook of medical and health sciences in developing countries: Education, practice, and research*. Cham, Switzerland: Springer International Publishing; 2023. pp. 1-24.
4. Latt NN, Putdivarnichapong W, Phetrasuwan S, Vongsirimas N. Factors predicting the intention of drug abuse avoidance among adolescents in Pinlaung Township, Myanmar: Predictive correlational design. *BMC Public Health*. 2024; 24: 8.
5. Clay KJ, Axelrod AE, MacLaughlin CM, Hooker JM. Light shining within the "Dark" classics: A perspective on entheogenic compounds. *ACS Chem Neurosci*. 2023; 14: 1697-1700.
6. Galanie S, Thodey K, Trenchard IJ, Filsinger Interrante M, Smolke CD. Complete biosynthesis of opioids in yeast. *Science*. 2015; 349: 1095-1100.
7. Gruba SM, Francis DH, Meyer AF, Spanolios E, He J, Meyer BM, et al. Characterization of the presence and function of platelet opioid receptors. *ACS Meas Sci Au*. 2022; 2: 4-13.
8. Khamooshi F, Doraji-Bonjar S, Akinnawo AS, Ghaznavi H, Salimi-Khorashad AR, Khamooshi MJ. Dark classics in chemical neuroscience: Comprehensive study on the biochemical mechanisms and clinical implications of opioid analgesics. *Chem Methodol*. 2023; 7: 964-993.
9. Khamooshi F, Akinnawo AS, Doraji-Bonjar S, Modarresi-Alam AR. Mitragynine chemistry: Extraction, synthesis, and clinical effects. *Chem Afr*. 2024; 7: 2907-2920.
10. Pathan H, Williams J. Basic opioid pharmacology: An update. *Br J Pain*. 2012; 6: 11-16.
11. Abdolmaleki S, Panjehpour A, Khaksar S, Ghadermazi M, Rostamnia S. Evaluation of central-metal effect on anticancer activity and mechanism of action of isostructural Cu(II) and Ni(II) complexes containing pyridine-2,6-dicarboxylate. *Eur J Med Chem*. 2023; 245: 114897.
12. Guo M, Bakhoda A, Gao ZG, Ramsey JM, Li Y, O'Connor KA, et al. Discovery of highly potent adenosine A(1) receptor agonists: Targeting positron emission tomography probes. *ACS Chem Neurosci*. 2021; 12: 3410-3417.
13. Hooker JM. Chemical neuroscience and the paths to impact. *ACS Chem Neurosci*. 2021; 12: 1.

14. Saran JS, Barbano RL, Schult R, Wiegand TJ, Selioutski O. Chronic diphenhydramine abuse and withdrawal: A diagnostic challenge. *Neurol Clin Pract.* 2017; 7: 439-441.
15. Shah M, Huecker MR. Opioid withdrawal. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2025.
16. Kelly ED, Andrew SH, Cecilia LB, Cassandra DG, Elise MW. Non-opioid neurotransmitter systems that contribute to the opioid withdrawal syndrome: A review of preclinical and human evidence. *J Pharmacol Exp Ther.* 2019; 371: 422-452.
17. Fadel ZH, Al-Azzawi AM. Design, synthesis and antimicrobial activity evaluation of new bisimidyl sulfonamido ketone comprising drug component. *Chem Methodol.* 2021; 5: 464-470.
18. Bahmani A, Taghvaei A, Firozian F, Chehardoli G. Folic acid as an exploiter of natural endocytosis pathways in drug delivery. *Chem Methodol.* 2024; 8: 96-122.
19. Hussain S, Alsinai A, Afzal D, Maqbool A, Afzal F, Cancan M. Investigation of closed formula and topological properties of remdesivir (C₂₇H₃₅N₆O₈P). *Chem Methodol.* 2021; 5: 485-497.
20. Asimakopoulou E, Zavridis P. Rehabilitation of chronic pain in post-critical care patients. A narrative review. *OBM Neurobiol.* 2023; 7: 194.
21. Northrup TF, Stotts AL, Green C, Potter JS, Marino EN, Walker R, et al. Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: A discrete survival and growth mixture model. *Addict Behav.* 2015; 41: 20-28.
22. Singh J, Gupta P. Drug addiction: Current trends and management. *Int J Indian Psychol.* 2017; 5: 2348-5396.
23. La Grua M, Sindaco G, Zanella M, Grazzini I, Musio A, Merlini A, et al. Is electrocatheter-mediated high-voltage pulsed radiofrequency of the dorsal root ganglion an effective adjuvant to epidural adhesiolysis in the treatment of chronic lumbosacral radicular pain? A retrospective analysis. *OBM Neurobiol.* 2023; 7: 171.
24. Ghodse H, Myles J, Smith SE. Clonidine is not a useful adjunct to methadone gradual detoxification in opioid addiction. *Br J Psychiatry.* 1994; 165: 370-374.
25. Gold MS. Opiate addiction and the locus coeruleus: The clinical utility of clonidine, naltrexone, methadone, and buprenorphine. *Psychiatr Clin N Am.* 1993; 16: 61-73.
26. Habibi MM, Mousavi M, Shekofteh-Gohari M, Parsaei-Khomami A, Hosseini MA, Haghani E, et al. Machine learning-enhanced drug testing for simultaneous morphine and methadone detection in urinary biofluids. *Sci Rep.* 2024; 14: 8099.
27. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: A review. *Am J Addict.* 2010; 19: 4-16.
28. Ziaaddini H, Nasirian M, Nakhaee N. Comparison of the efficacy of buprenorphine and clonidine in detoxification of opioid-dependents. *Addict Health.* 2012; 4: 79-86.
29. Applewhite D, Regan S, Koenigs K, Mackin S, Schmidt C, Wakeman SE. Use of promethazine, gabapentin and clonidine in combination with opioids or opioid agonist therapies among individuals attending a syringe service program. *Int J Drug Policy.* 2020; 79: 102752.
30. Nakagawa A, Matsumura E, Koyanagi T, Katayama T, Kawano N, Yoshimatsu K, et al. Total biosynthesis of opiates by stepwise fermentation using engineered *Escherichia coli*. *Nat Commun.* 2016; 7: 10390.
31. Gerra G, Ceresini G, Rastelli G, Butturini L, Vescovi PP. Effect of diclofenac on the opiate withdrawal syndrome. *G Clin Med.* 1985; 66: 459-465.

32. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. *Am J Addict.* 2019; 28: 55-62.
33. Dunbar SA, Karamov IG, Buerkle H. The effect of spinal ibuprofen on opioid withdrawal in the rat. *Anesth Analg.* 2000; 91: 417-422.
34. Assadi SM, Radgoodarzi R, Ahmadi-Abhari SA. Baclofen for maintenance treatment of opioid dependence: A randomized double-blind placebo-controlled clinical trial [ISRCTN32121581]. *BMC Psychiatry.* 2003; 3: 16.
35. Weisman S. Naproxen for post-operative pain. *J Pharm Pharm Sci.* 2021; 24: 62-70.
36. Zucker AH. Clinical results with methocarbamol in opiate withdrawal. *Am J Med Sci.* 1959; 237: 190-193.
37. Tancawan AL, Pato MN, Abidin KZ, Asari AS, Thong TX, Kochhar P, et al. Amoxicillin/clavulanic acid for the treatment of odontogenic infections: A randomised study comparing efficacy and tolerability versus clindamycin. *Int J Dent.* 2015; 2015: 472470.
38. Gander T, Bingol AS, Mascolo L, Grätz KW, Lübbers HT. Infection after dental intervention. Iatrogenic or general medical cause? Case report. *Schweiz Monatsschr Zahnmed.* 2013; 123: 19-31.
39. Castellani Nicolini N, Belfiore J, Biancofiore G. Multimodal pain management of liver transplantation: What is new? *OBM Transplant.* 2023; 7: 198.
40. Giustino V. Pain and neurobiology. *OBM Neurobiol.* 2024; 8: 210.
41. Evans AG, Burns BL, Ibrahim MM, Kesayan T, Brooks-Horror KN, Assi PE, et al. Headache frequency and pain severity following a nerve stimulator implant for chronic migraine: A systematic review and meta-analysis. *OBM Neurobiol.* 2023; 7: 170.
42. Ryan L, Beer H, Thomson E, Philcox E, Kelly C. Autistic traits correlate with chronic musculoskeletal pain: A self-selected population based survey. *OBM Neurobiol.* 2023; 7: 155.
43. Kemény LV, Robinson KC, Hermann AL, Walker DM, Regan S, Yew YW, et al. Vitamin D deficiency exacerbates UV/endorphin and opioid addiction. *Sci Adv.* 2021; 7: eabe4577.
44. Hosseinzadeh A, Kamrava SK, Joghataei MT, Darabi R, Shakeri-Zadeh A, Shahriari M, et al. Apoptosis signaling pathways in osteoarthritis and possible protective role of melatonin. *J Pineal Res.* 2016; 61: 411-425.
45. Stein C. Opioid receptors. *Annu Rev Med.* 2016; 67: 433-451.
46. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, et al. Orphanin FQ: A neuropeptide that activates an opioidlike G protein-coupled receptor. *Science.* 1995; 270: 792-794.
47. Herbert M, Holzer P. Warum versagen substanz P (NK1)-rezeptorantagonisten in der schmerztherapie? *Anaesthesist.* 2002; 51: 308-319.
48. Sacerdote P, Levrini L. Peripheral mechanisms of dental pain: The role of substance P. *Mediat Inflamm.* 2012; 2012: 951920.
49. Chang CT, Jiang BY, Chen CC. Ion Channels involved in substance P-mediated nociception and antinociception. *Int J Mol Sci.* 2019; 20: 1596.
50. Patterson DR, Ptacek JT, Carrougheer GJ, Sharar SR. Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. *Pain.* 1997; 72: 367-374.
51. Vardanyan RS, Hruby VJ. Chapter 5-Anxiolytics (Tranquilizers). In: *Synthesis of essential drugs.* Amsterdam, The Netherlands: Elsevier; 2006. pp. 69-82.

52. Gray AM. Effect of alprazolam on opiate withdrawal: A combined behavioural and microdialysis study. *Eur J Pharmacol*. 1996; 313: 73-77.
53. Das S. Detoxification of drug and substance abuse. London, UK: IntechOpen; 2020.
54. Burrows DL, Hagardorn AN, Harlan GC, Wallen ED, Ferslew KE. A fatal drug interaction between oxycodone and clonazepam. *J Forensic Sci*. 2003; 48: 683-686.
55. Nunes EV, Quitkin FM, Donovan SJ, Deliyannides D, Ocepek-Welikson K, Koenig T, et al. Imipramine treatment of opiate-dependent patients with depressive disorders: A placebo-controlled trial. *Arch Gen Psychiatry*. 1998; 55: 153-160.
56. de Gandarias JM, Echevarria E, Acebes I, Silio M, Casis L. Effects of imipramine administration on mu-opioid receptor immunostaining in the rat forebrain. *Arzneimittelforschung*. 1998; 48: 717-719.
57. Onali P, Dedoni S, Olinas MC. Direct agonist activity of tricyclic antidepressants at distinct opioid receptor subtypes. *J Pharmacol Exp Ther*. 2010; 332: 255-265.
58. Amelin AV, Skoromets AA, Korenko LA, Tumelevich B, Gonchar MA. A comparative efficiency of amitriptyline, fluoxetine and maprotiline in prevention of migraine in attack-free period. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2000; 100: 20-23.
59. Kerrick JM, Fine PG, Lipman AG, Love G. Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: A placebo-controlled trial. *Pain*. 1993; 52: 325-330.
60. Wells BG, Gelenberg AJ. Chemistry, pharmacology, pharmacokinetics, adverse effects, and efficacy of the antidepressant maprotiline hydrochloride. *Pharmacotherapy*. 1981; 1: 121-138.
61. Hesketh SA, Brennan AK, Jessop DS, Finn DP. Effects of chronic treatment with citalopram on cannabinoid and opioid receptor-mediated G-protein coupling in discrete rat brain regions. *Psychopharmacology*. 2008; 198: 29-36.
62. Goyal P, Kattula D, Rao R, Bhad R, Mishra AK, Dhawan A. Trazodone for sleep disturbance in opioid dependent patients maintained on buprenorphine: A double blind, placebo-controlled trial. *Drug Alcohol Depend*. 2023; 250: 110891.
63. Tang L, Shukla PK, Wang ZJ. Trifluoperazine, an orally available clinically used drug, disrupts opioid antinociceptive tolerance. *Neurosci Lett*. 2006; 397: 1-4.
64. Auld F, Maschauer EL, Morrison I, Skene DJ, Riha RL. Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. *Sleep Med Rev*. 2017; 34: 10-22.
65. Masters A, Pandi-Perumal SR, Seixas A, Girardin JL, McFarlane SI. Melatonin, the hormone of darkness: From sleep promotion to Ebola treatment. *Brain Disord Ther*. 2014; 4: 1000151.
66. Gunja N. The clinical and forensic toxicology of Z-drugs. *J Med Toxicol*. 2013; 9: 155-162.
67. Moskowitz MA, Cutrer FM. SUMATRIPTAN: A receptor-targeted treatment for migraine. *Annu Rev Med*. 1993; 44: 145-154.
68. Zullino DF, Cottier AC, Besson J. Topiramate in opiate withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002; 26: 1221-1223.
69. Guglielmo R, Kobylinska L, de Filippis R. Topiramate, naltrexone, and acamprosate in the treatment of alcohol use disorders. In: *NeuroPsychopharmacotherapy*. Cham, Switzerland: Springer International Publishing; 2020. pp. 1-16.
70. Banafshe HR, Hajhashemi V, Minaiyan M, Mesdaghinia A, Abed A. Antinociceptive effects of maprotiline in a rat model of peripheral neuropathic pain: Possible involvement of opioid system. *Iran J Basic Med Sci*. 2015; 18: 752-757.

71. Jacob RG, Holmstrand J, Eriksson JH, Anggård E. Propranolol in the treatment of opiate dependence—A controlled study. *Psychopharmacologia*. 1975; 41: 71-73.
72. Fayyazi A, Khajeh A, Ghazavi A, Sangestani M. Omega 3 in childhood migraines: A double blind randomized clinical trial. *Iran J Child Neurol*. 2016; 10: 9-13.
73. Scuteri D, Tonin P, Corasaniti MT, Bagetta G. Targeting neuroplasticity for the management of pain and agitation in Alzheimer's disease via bergamot nanotherapy. *OBM Neurobiol*. 2022; 6: 133.
74. Buydens-Branchey L, Branchey M, Reel-Brander C. Efficacy of buspirone in the treatment of opioid withdrawal. *J Clin Psychopharmacol*. 2005; 25: 230-236.
75. Navidian A, Mobaraki H, Shakiba M. The effect of education through motivational interviewing compared with conventional education on self-care behaviors in heart failure patients with depression. *Patient Educ Couns*. 2017; 100: 1499-1504.
76. Galligan JJ, Akbarali HI. Molecular physiology of enteric opioid receptors. *Am J Gastroenterol Suppl*. 2014; 2: 17-21.
77. Kosten TR, George TP. The neurobiology of opioid dependence: Implications for treatment. *Sci Pract Perspect*. 2002; 1: 13-20.
78. Camilleri M. Serotonin in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes*. 2009; 16: 53-59.
79. Krystal JH, Staley J, Mason G, Petrakis IL, Kaufman J, Harris RA, et al. γ -aminobutyric acid type A receptors and alcoholism: Intoxication, dependence, vulnerability, and treatment. *Arch Gen Psychiatry*. 2006; 63: 957-968.
80. Koob GF, Kandel DB, Baler RD, Volkow ND. Neurobiology of addiction. In: *Tasman's Psychiatry*. Cham, Switzerland: Springer International Publishing; 2020. pp. 1-51.
81. Koob GF, Volkow ND. Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*. 2016; 3: 760-773.
82. Glatt MM. The treatment of the withdrawal stage in narcotic addicts by diphenoxylate and chlormethiazole. *Int J Addict*. 1972; 7: 593-596.
83. Ives TJ, Stults CC. Short-course diphenoxylate hydrochloride for treatment of methadone withdrawal symptoms. *Br J Psychiatry*. 1983; 143: 513-514.
84. Lee VR, Vera A, Alexander A, Ruck B, Nelson LS, Wax P, et al. Loperamide misuse to avoid opioid withdrawal and to achieve a euphoric effect: High doses and high risk. *Clin Toxicol*. 2019; 57: 175-180.
85. Negro S, Reyes R, Azuara ML, Sánchez Y, Barcia E. Morphine, haloperidol and hyoscine N-butyl bromide combined in s.c. infusion solutions: Compatibility and stability. Evaluation in terminal oncology patients. *Int J Pharm*. 2006; 307: 278-284.
86. Tytgat GN. Hyoscine butylbromide: A review of its use in the treatment of abdominal cramping and pain. *Drugs*. 2007; 67: 1343-1357.
87. Passos ID, Mironidou-Tzouveleki M. Chapter 71—Hallucinogenic plants in the mediterranean countries. In: *Neuropathology of drug addictions and substance misuse*. San Diego, CA: Academic Press; 2016. pp. 761-772.
88. Mahikhan F, Hashemian M, Dehesh T, Jafari E, Jafari M, Rahimi HR. Impact of ondansetron on withdrawal signs, fentanyl requirement and pain relief in opioid-addicted patients under general anesthesia. *Curr Clin Pharmacol*. 2019; 14: 232-241.

89. Carr KD, Hiller JM, Simon EJ. Diphenhydramine potentiates narcotic but not endogenous opioid analgesia. *Neuropeptides*. 1985; 5: 411-414.
90. Gurtu S. Mu receptor-serotonin link in opioid induced hyperactivity in mice. *Life Sci*. 1990; 46: 1539-1544.
91. Baraniuk JN. Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. *J Allergy Clin Immunol*. 1992; 90: 1045-1050.
92. Katzung BG. Basic and clinical pharmacology. 14th ed. New York, NY: McGraw-Hill Education; 2017.
93. McPherson RA, Pincus MR. Henry's clinical diagnosis and management by laboratory methods e-book. Elsevier; 2021.
94. Ghaznavi H, Mohammadghasemipour Z, Shirvaliloo M, Momeni MK, Metanat M, Gorgani F, et al. Short-term celecoxib (celebrex) adjuvant therapy: A clinical trial study on COVID-19 patients. *Inflammopharmacology*. 2022; 30: 1645-1657.
95. Anwari JS, Iqbal S. Antihistamines and potentiation of opioid induced sedation and respiratory depression. *Anaesthesia*. 2003; 58: 494-495.
96. Pauline De B, Thierry C, Koen B, Els M, Myriam Van W. Are antihistamines effective in children? A review of the evidence. *Arch Dis Child*. 2017; 102: 56-60.
97. Suzuki T, Mori T, Tsuji M, Misawaa M, Onodera K. Generalization of D-, L- and DL-chlorpheniramine and zolantidine to the discriminative stimulus effects of cocaine and methamphetamine. *Behav Pharmacol*. 1997; 8: 718-724.
98. Erlendson MJ, D'Arcy N, Encisco EM, Yu JJ, Rincon-Cruz L, Peltz G, et al. Palonosetron and hydroxyzine pre-treatment reduces the objective signs of experimentally-induced acute opioid withdrawal in humans: A double-blinded, randomized, placebo-controlled crossover study. *Am J Drug Alcohol Abuse*. 2017; 43: 78-86.
99. Clonidine/hydroxyzine/opioids withdrawal. *React Weekly*. 2023; 1938: 416.
100. Capasso A, Pinto A, Sorrentino L, Cirino G. Dexamethasone inhibition of acute opioid physical dependence in vitro is reverted by anti-lipocortin-1 and mimicked by anti-type II extracellular PLA2 antibodies. *Life Sci*. 1997; 61: PL127-PL134.
101. Eglen RM. Overview of muscarinic receptor subtypes. *Handb Exp Pharmacol*. 2012; 208: 3-28.
102. Simons FE, Simons KJ. Histamine and H1-antihistamines: Celebrating a century of progress. *J Allergy Clin Immunol*. 2011; 128: 1139-1150.e4.
103. Kleber HD, Gold MS, Riordan CE. The use of clonidine in detoxification from opiates [Internet]. Vienna, Austria: United Nations Office On Drugs and Crime; 1980. Available from: https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1980-01-01_2_page002.html.
104. Doughty B, Morgenson D, Brooks T. Lofexidine: A newly FDA-approved, nonopioid treatment for opioid withdrawal. *Ann Pharmacother*. 2019; 53: 746-753.
105. Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database Syst Rev*. 2017. doi: 10.1002/14651858.CD002021.pub4.
106. Sofuoglu M, DeVito EE, Carroll KM. Pharmacological and behavioral treatment of opioid use disorder. *Psychiatr Res Clin Pract*. 2018; 1: 4-15.
107. Khadish S, Navidian A, Momeni MK, Zolfaghari Z, Khayyati R. The Effect of cognitive-emotional training on post-traumatic stress and growth in discharged patients with COVID-19. *Med Surg Nurs J*. 2023; 12: e141927.

108. Resnick A, Bergman A, Oberman R, Taylor SL, Chuang E, Cummings K, et al. Knowledge and attitudes towards use of complementary and integrative health therapies for veterans with opioid use disorder in the veterans health administration. *OBM Integr Complement Med*. 2024; 9: 012.
109. Roberto KA, Teaster PB, Fua I. Opioid-involved elder abuse in the united states: Perspectives from adult protective services. *OBM Geriatr*. 2025; 9: 294.
110. LeQuang JA, Pergolizzi JJ. Aging high: Opioid use disorder in the elderly population. *OBM Geriatr*. 2019; 3: 047.
111. Pozzi G, Conte G, De Risio S. Combined use of trazodone-naltrexone versus clonidine-naltrexone in rapid withdrawal from methadone treatment. A comparative inpatient study. *Drug Alcohol Depend*. 2000; 59: 287-294.
112. Sevarino KA, Kosten TR. Naltrexone for initiation and maintenance of opiate abstinence. In: *Opiate receptors and antagonists: From bench to clinic*. Totowa, NJ: Humana Press; 2009. pp. 227-245.
113. Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S. Prescribing naloxone to actively injecting heroin users. *J Addict Dis*. 2006; 25: 89-96.
114. Goa KL, Wagstaff AJ. Losartan potassium: A review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs*. 1996; 51: 820-845.
115. Miyagawa S, Yamada H, Matsubara H. Long-term antihypertensive efficacy of losartan/hydrochlorothiazide combination therapy on home blood pressure control. *Clin Exp Hypertens*. 2012; 34: 439-446.
116. Nekooeian AA, Rasti Pour A, Dehghani F, Mashghoolozekr E, Esmaeilpour T. Effects of captopril and losartan on cardiac stereology in rats with renovascular hypertension. *Iran J Med Sci*. 2021; 46: 169-179.
117. Gold MS, Pottash AL, Extein I, Kleber HD. Clonidine and opiate withdrawal. *Lancet*. 1980; 2: 1078-1079.
118. Kapusta DR, Obih JC. Central kappa opioid receptor-evoked changes in renal function in conscious rats: Participation of renal nerves. *J Pharmacol Exp Ther*. 1993; 267: 197-204.
119. Kapusta DR, Obih JC, Dibona GF. Central mu opioid receptor-mediated changes in renal function in conscious rats. *J Pharmacol Exp Ther*. 1993; 265: 134-143.
120. Pechnick RN. Effects of opioids on the hypothalamo-pituitary-adrenal axis. *Annu Rev Pharmacol Toxicol*. 1993; 33: 353-382.
121. Holaday JW. Cardiovascular effects of endogenous opiate systems. *Annu Rev Pharmacol Toxicol*. 1983; 23: 541-594.
122. Stefano GB, Scharrer B, Smith EM, Hughes Jr TK, Magazine HI, Bilfinger TV, et al. Opioid and opiate immunoregulatory processes. *Crit Rev Immunol*. 1996; 16: 109-144.
123. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*. 2006; 58: 389-462.
124. Mishra S, Bentley-Hewitt K, Lubransky A, Venn B, Hedderley D, Dinnan H, et al. Metabolic, anthropometric and blood pressure effects of adding two kiwifruit or bottled water into the diets of people with pre-diabetes: A randomised, parallel group, intervention study. *Recent Prog Nutr*. 2022; 2: 006.
125. Dhawan K, Dhawan S, Sharma A. Passiflora: A review update. *J Ethnopharmacol*. 2004; 94: 1-23.

126. Bent S, Padula A, Moore D, Patterson M, Mehling W. Valerian for sleep: A systematic review and meta-analysis. *Am J Med.* 2006; 119: 1005-1012.
127. Soltaninejad M, Amleshi RS, Shabani M, Ilaghi M. Unraveling the protective effects of curcumin against drugs of abuse. *Heliyon.* 2024; 10: e30468.
128. Choi J, Kim TH, Choi TY, Lee MS. Ginseng for health care: A systematic review of randomized controlled trials in Korean literature. *PLoS One.* 2013; 8: e59978.
129. Tate S. Peppermint oil: A treatment for postoperative nausea. *J Adv Nurs.* 1997; 26: 543-549.
130. Amsterdam JD, Shults J, Soeller I, Mao JJ, Rockwell K, Newberg AB. Chamomile (*Matricaria recutita*) may provide antidepressant activity in anxious, depressed humans: An exploratory study. *Altern Ther Health Med.* 2012; 18: 44-49.
131. Pengelly A, Snow J, Mills SY, Scholey A, Wesnes K, Butler LR. Short-term study on the effects of rosemary on cognitive function in an elderly population. *J Med Food.* 2012; 15: 10-17.
132. Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (*Crocus sativus* L.) and major depressive disorder: A meta-analysis of randomized clinical trials. *J Integr Med.* 2013; 11: 377-383.
133. Unno K, Furushima D, Nomura Y, Yamada H, Iguchi K, Taguchi K, et al. Antidepressant effect of shaded white leaf tea containing high levels of caffeine and amino acids. *Molecules.* 2020; 25: 3550.
134. Farzin D, Mousavi E. Effects of harmaline, norharmaline and harmine on writhing behavior induced by acetic acid in mice. *J Guilan Univ Med Sci.* 2011; 19: 29-37.
135. Glennon RA, Lee M, Rangisetty JB, Dukat M, Roth BL, Savage JE, et al. 2-Substituted tryptamines: Agents with selectivity for 5-HT₆ serotonin receptors. *J Med Chem.* 2000; 43: 1011-1018.
136. Aricioglu F, Altunbas H. Harmaline induces anxiolysis and antidepressant-like effects in rats. *Ann N Y Acad Sci.* 2003; 1009: 196-201.
137. Liu J, Zhang Q, Tao T, Wang LY, Sun JY, Wu CJ, et al. Health benefits of spices in individuals with chemotherapeutic drug-induced cardiotoxicity. *Curr Opin Pharmacol.* 2022; 63: 102187.
138. Singh D, Müller CP, Vicknasingam BK. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend.* 2014; 139: 132-137.
139. Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, et al. From Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev.* 2013; 37: 138-151.
140. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: An emerging botanical agent with stimulant, analgesic and opioid-like effects. *J Am Osteopath Assoc.* 2012; 112: 792-799.
141. Khamooshi F, Mousavi SM, Doraji-Bonjar S, Zolfigol M. Anti-HIV drugs study: Study of NNRTIs function and overview synthesis of specific and rare aryloxy tetrazoles derivatives as NNRTIs and Anti-HIV drug. *Medicon Pharm Sci.* 2022; 2: 4-10.
142. Khamooshi F, Haghighi Kekhaiye-Jhaleh B, Aryan R, Alam AM, Rezvani AR, et al. Solvent-free preparation of 5-aryloxytetrazoles *via* [2 + 3] cycloaddition of cyanates and sodium azide using silica supported sulfuric acid as an effective heterogeneous catalyst. *Chem Heterocycl Compd.* 2014; 49: 1464-1468.
143. Modarresi-Alam AR, Khamooshi F. A one-pot synthesis of Aryl-N-[(4-methylphenylsulfonyl)]-N-(triphenylphosphoranylidene)imidocarbamates from 5-Aryloxytetrazoles. *Synth Commun.* 2004; 34: 129-135.

144. Khamooshi F, Modarresi-Alam AR. Solvent-free preparation of arylaminotetrazole derivatives using Aluminum(III) hydrogensulfate as an effective catalyst. *Chin Chem Lett.* 2010; 21: 892-896.
145. Modarresi-Alam AR, Keykha H, Khamooshi F, Dabbagh HA. Dynamic ¹H NMR study of 4-methylphenoxyimidoyl azides: Conformational or configurational isomerisation? *Tetrahedron.* 2004; 60: 1525-1530.
146. Modarresi-Alam AR, Khamooshi F, Nasrollahzadeh M, Amirazizi HA. Silica supported perchloric acid (HClO₄-SiO₂): An efficient reagent for the preparation of primary carbamates under solvent-free conditions. *Tetrahedron.* 2007; 63: 8723-8726.
147. Sunbal, Alamzeb M, Omer M, Abid OU, Ullah M, Sohail M, et al. Chemical insights into the synthetic chemistry of five-membered saturated heterocycles-A transition metal-catalyzed approach. *Front Chem.* 2023; 11: 1185669.
148. Varvounis G, Gerontitis I, Gkalpinos V. Metal-catalyzed synthesis of five-membered ring N-heterocycles. A recent update. *Chem Heterocycl Compd.* 2018; 54: 249-268.
149. Kaur DN, Bhardwaj P, Gupta M. Recent developments in the synthesis of five- and six-membered N-heterocycles from dicarbonyl compounds. *Curr Org Chem.* 2021; 25: 2765-2790.
150. Modarresi-Alam AR, Nasrollahzadeh M, Khamooshi F. Solvent-free preparation of primary carbamates using silica sulfuric acid as an efficient reagent. *Arkivoc.* 2007; 16: 238-245.
151. Modarresi-Alam AR, Khamooshi F, Rostamizadeh M, Keykha H, Nasrollahzadeh M, Bijanzadeh HR, et al. Dynamic ¹H NMR spectroscopic study of the restricted SN rotation in aryl-N-(arylsulfonyl)-N-(triphenylphosphoranylidene)imidocarbamates. *J Mol Struct.* 2007; 841: 61-66.
152. Ritter JM, Flower RJ, Henderson G, Loke YK, MacEwan D, Rang HP. *Rang y dale. Farmacología.* Elsevier Health Sciences; 2020.
153. Stahl SM. *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications.* 5th ed. Cambridge, UK: Cambridge University Press; 2021.
154. Carey FA, Sundberg RJ. *Advanced organic chemistry: Part A: Structure and mechanisms.* Springer; 2007.
155. Modaresi AA, Nasr EM, Khamoushi F. Al(HSO₄)₃ mediated for the preparation of primary carbamates under solvent-free conditions. *Sci Iran.* 2008; 15: 452-455.
156. Fahad MM, Shafiq N, Arshad U, Radhi AJ. As antimicrobial agents: Synthesis, structural characterization and molecular docking studies of barbituric acid derivatives from phenobarbital. *Chem Methodol.* 2022; 6: 122-136.
157. Jampilek J. Heterocycles in medicinal chemistry. *Molecules.* 2019; 24: 3839.
158. Modarresi-Alam AR, Shariati I, Khamooshi F, Doraji-Bonjar S. Acid concentration, low- and high-valent sulfate anion, and solvent effects on polaronic transitions and conductivity of new poly (*ortho*-methoxyaniline) nanocomposites. *Polym Bull.* 2025; 82: 3225-3249.
159. Modarresi-Alam AR, Khamooshi F, Pakseresht M, Soleimani M, Doraji-Bonjar S, Shabzendedar S, et al. Important effects on polaronic transitions in new nanocomposites from polyaniline and silica. *J Mol Struct.* 2025; 1336: 142016.
160. Khamooshi F, Haghighi Kekhaiye-Jhaleh B. ZnCl₂/AlCl₃/Silica (ZAS) as an effective heterogeneous catalyst for the synthesis of 5-Aryloxy tetrazoles. *Chem J Mold.* 2012; 7: 130-135.

161. Kalamarides DJ, Singh A, Dani JA. Protracted opioid withdrawal behaviors are reduced by nitric oxide inhibition in mice. *Addict Neurosci.* 2024; 12: 100167.
162. Wang SC, Chen YC, Lee CH, Cheng CM. Opioid addiction, genetic susceptibility, and medical treatments: A review. *Int J Mol Sci.* 2019; 20: 4294.
163. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: Pharmacological and psychosocial interventions to treat opioid addiction. *Clin Psychol Rev.* 2010; 30: 155-166.
164. Torres-Lockhart KE, Lu TY, Weimer MB, Stein MR, Cunningham CO. Clinical management of opioid withdrawal. *Addiction.* 2022; 117: 2540-2550.
165. Almeida A, Conway M, Grelotti DJ, Gupta A, Frank D, Bórquez A. Medication experiences in the treatment of opioid use disorders: Insights from Reddit. *Addiction.* 2025. doi: 10.1111/add.70022.
166. Vining E, Kosten TR, Kleber HD. Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. *Br J Addict.* 1988; 83: 567-575.
167. Mitchell TB, White JM, Somogyi AA, Bochner F. Slow-release oral morphine versus methadone: A crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction.* 2004; 99: 940-945.
168. Schumaker A, Klauber R, Aasen M, Padua M, Meresh E. Alcohol withdrawal induced malignant catatonia and response to bromocriptine: Case report. *OBM Neurobiol.* 2022; 6: 121.
169. RxFiles. Prescription for managing opioid withdrawal [Internet]. Saskatoon, SK, Canada: RxFiles. Available from: <https://www.rxfiles.ca/rxfiles/uploads/documents/members/Opioid-Withdrawal-Rx.docx>.
170. Cardiff and Vale University Health Board. Guidelines for the management of opioid-dependent individuals admitted to UHB hospitals [Internet]. Cardiff and Vale University Health Board; 2019. Available from: <https://cavuhb.nhs.wales/files/policies-procedures-and-guidelines/patient-safety-and-quality/g-patient-safety/uhb-328-guidelines-for-the-management-of-opioid-dependents/>.