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REVIEW ARTICLE

The common neurological basis and targeted therapeutic approaches for chronic pain and opioid addiction.

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Abstract

Chronic pain and drug addiction seriously threaten human health and generate a large loss of labor. Most highly addictive drugs are derived from opioids, which have severe side effects and are difficult to quit completely. On the other hand, opioid analgesics are widely used in detoxification for opioid addiction. These opioids are effective for controlling acute withdrawal symptoms, but can be problematic under long-term usage as maintenance therapy. Both chronic pain and opioid abuse are related to neurotransmitters and central reward pathways in the brain. As to provide new weapons for defending human health, this article summarized the similarities and differences between chronic pain and opioid addiction, based on their common neurobiological basis, and discussed the breakthroughs in targeted therapeutic approaches. Furthermore, we have brought out an innovative and integrative therapeutic scheme by combining drugs, medical devices, and phycological / behavioral therapies, according to the patient's individual situation, aiming at achieving better effects against these two types of diseases.

INTRODUCTION

The social impact of drug addiction and chronic pain

The opiates obtained from the berries of opium poppy have analgesic, hypnotic, antitussive, and antidiarrheal properties and are still used by doctors for controlling various clinical symptoms. Opioid is a double-edged sword. If used for medical purposes, it is an angelic drug to relieve human suffering, while if used for hedonic purposes (that aiming at only pursuing pleasure and illusion), it will drag users into the abyss of drug dependence.

The symptoms occurring under opioid withdrawal can severely affect the quality of life in patients after the development of physical dependence. Abusing opioids can produce euphoria, but as the window is narrow, opioid addicted patents can be easily overdosed that causing breath inhibition and even death, if the rescue procedures are not taken in time. In the United States, more people die each year from drug overdose than from the Vietnam War. Drug overdose resulted in 107622 deaths during 2021 (surpassing the number of deaths caused by gun crimes or car accidents); among these, 80816 (75.1%) involved opioids (CDC, 2022), and the number still increases at a high speed.

According to International Narcotics Control Board of the United Nations, 10 percent of the world's population is involved in the production, distribution, and consumption of drugs. At least 200 million people in the world have used drugs at least for one time. About 200 000 people die from drug overdose and 10 million people lose their working capabilities because of drug abuse each year, (Qin *et al.* 1999; Liu & Lin, 2008).

Among the existing drugs, opiates such as heroin are the most harmful. Opioid addiction has led to many serious social problems. These drugs are highly addictive and are associated with severe withdrawal symptoms. The completion of withdrawal can last as long as several months. After this period the physical dependance might be relieved in opioid addicted patients. However, the psychological dependance is hard to get rid of and contributing to craving and drug relapse. At present, there is no effective method to prevent relapse of opioid dependence. The relapse rate is as high as 95% after 6 months of withdrawal (Liu & Lin, 2008).

Chronic pain refers to pain that lasts more than 3 months, including scenarios such as neuropathic pain, fibromyalgia, cancer pain, and chronic arthritic pain (Treede *et al.* 2019). Similar to drug addiction, chronic pain also has a great negative impact on the society. Regardless of the substantial medical progress has been made in recent decades, management of chronic pain is still one of the most pressive clinical challenges.

At an individual level, chronic pain restricts patients' essential daily activities such as eating, sleeping, and exercising. Due to constant pain, the quality of life of patients is seriously reduced, resulting in complete loss of working capabilities in severe case (Mills *et al.* 2019). At the society level, chronic pain has imposed a huge ecconomical burden on the public healthcare system. Approximately 100 million people in the United States are affected by chronic pain conditions. A study in 2021 showed that pain-induced socioeconomic loss in the United States was estimated to be $296 billion per year, which is greater than cardiovascular disease, cancer, or diabetes (Yong *et al.* 2021). In China, chronic pain affects around 400 million patients (Zheng *et al.* 2020). However, less than 60% of them sought for medical help and only 20% of them reached sufficient pain relief after therapy (Chen *et al.* 2016).

Currently, chronic pain therapy is largely based on anticonvulsants and tricyclic antidepressants. However, their therapeutic efficacy is unsatisfactory (Gordh *et al.* 2008; Moore *et al.* 2015). The lack of effective treatment for chronic pain patients has become an urgent social problem to be addressed. On the other hand, although opioids can produce good analgesia, they can also induce strong tolerance and dependence, which has led to addiction under continuous usage, limiting their usage as a long-term solution (Mercadante *et al.* 2019; Vowles *et al.* 2015). Furthermore, improper usage of opioids in a large number of patients and inadequate restrictions on prescription of opioids as pain killers in recent years, has led to an ongoing opioid crisis, especially in western countries (Birnbaum *et al.* 2011).

Both drug users and patients with chronic pain are difficult to return to society, resulting in a large impairment of labor forces and immeasurable social and economic losses.

Opioid analgesics are a class of drugs that are heavily abused

Opioids primarily being used for pain relief. Ever since their discovery, they have been closely associated with adverse events such as addiction (Kosten & Baxter, 2019). The majority of highly abusive substances are also coming from opioid analgesics (Stein, 2013) (Table 1).

Morphine can induce quick and effective pain relief. Application of morphine also reduced the discomfort, irritability, shortness of breath, and palpitations caused by pain. However, morphine cannot be used repeatedly. Even at low dosages, chronic usage of morphine (for 1 to 2 weeks) can lead to physical dependance. Withdrawal symptoms such as irritability, insomnia, muscle tremor, vomiting, abdominal pain, dilated pupils, runny nose, and sweating will occur immediately after the cessation of morphine application (Listos *et al.* 2019).

Morphine was deployed to synthesize heroin in the late 19th century (Sulaiman *et al.* 2018), which was originally used for sedation, analgesia, and treating cough. But as users became more fall back on its hedonic efficacy, heroin became a major drug of abuse (Suwanwela & Poshyachinda, 1986). Overall, there were more than 2.7 million opioid-dependent patients in the United States in 2020. More than half a million of these patients

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Tab. 1. Commonly used analgesics that are prone to be abused after repeated usage; more plus (+) signs indicate greater addiction.

Drug	Type	Indication	Abuse Proneness
Morphine	μopioid receptor agonist	Relief of severe acute pain	+++
Heroin	μopioid receptor agonist	Relief of moderate to severe pain	++++
Oxycodone	μopioid receptor agonist	Relief of moderate to severe pain	+++
Methadone	μopioid receptor agonist	Relief of severe pain	++++
Buprenorphine	Partial μopioid receptor agonist	Relief of moderate to severe pain	++
Hydroxymorphone	μopioid receptor agonist	Relief of moderate to severe pain	++++
Fentanyl	μopioid receptor agonist	Relief of moderate to severe pain	++++
Dolantine	μopioid receptor agonist	Relief of moderate to severe pain	++
Codeine	μopioid receptor agonist	Relief of moderate pain	+
Hydrocodone	μopioid receptor agonist	Relief of moderate to severe pain	+
Dihydroetorphine	μopioid receptor agonist	Relief of severe acute pain	+++

abusing heroin. The great physical dependence together with other side effects produced by heroin resulted in the situation that it is that basically impossible to quit and extremely easy to relapse. Over 19% of all opioid overdose deaths in 2020 is related heroin abuse (CDC, 2023).

Another commonly abused opioid analgesic is oxycodone, which is used to treat moderate to severe pain, as well as chronic pain. Oxycodone is highly addictive, especially under long-term application, thus needs to be prescribed with caution. Oxycodone was the leading cause of death from drug overdose in the United States until 2012. Withdrawal from oxycodone is difficult. Only in 2011, about 14,000 patients in the United States were sent for emergency treatment due to suicide attempts as a result of oxycodone withdrawal (Warner *et al.* 2016).

In 2003, the State Food and Drug Administration of China has clarified the rules for the use of oxycodone. The rules stipulate that doctors must establish a long-term relationship with the patient, prescribe the drug only if the patient has no prior history of opioid addiction, and the number should not exceed 15 days at a time. In addition, the continuous usage of oxycodone cannot be longer than 8 weeks.

Oxymorphone is similar to oxycodone but is twice as potent. Oxymorphone sustained-release agents are mainly used to treat sustained pain and spontaneous pain, that are difficult to be suppressed by other drugs (Prommer, 2006). The drug was approved by the Food and Drug Administration (FDA) in 2006. However, in 2012, Endo Pharmaceuticals changed the formulation of oxymorphone sustained-release agents, so that some patients were able to inject oxymorphone directly and resulted in the outbreak of severe hepatitis C, HIV and blood diseases (Peters *et al.* 2016).

On June 8, 2017, the FDA ordered the manufacturer, Endo Pharmaceuticals, to stop selling its powerful opioid pain reliever, the sustained-release version of oxymorphone (Opana ER). It is the first time FDA has ordered an opioid painkiller to be removed from shelves based on the potential of drug abuse harming public health. The example of oxymorphone demonstrates that the risk of abuse for some opioid analgesics already outweighs their benefits of analgesic utility.

Fentanyl is a powerful analgesic used for the treatment of severe pain such as cancer-induced pain, but with a rapid onset and a short duration of action. As a potent μ-opioid receptor agonist, fentanyl is 50-100 times more effective than morphine, and some fentanyl analogues such as carfentanil can even reach 10,000 times of the analgesic strength of morphine (and 100 times of the strength of heroin).

The demand for heroin in the US drug market has increased dramatically over the past decade. One important reason is that fentanyl or its equivalents were added into heroin to produce lower price heroin (Kuczyńska *et al.* 2018). However, as a consequence, heroin users are becoming more easily to get overdosed. The mortality rate of heroin overdose in the United States in 2014 has become more than three times of that in 2010, and as a result, heroin reached highest in overdose fatality rate among all abused drugs (Warner *et al.* 2016).

Methadone and buprenorphine are also analgesic opioids used for the management of moderate to severe pain, but they can also produce addiction. In particular, methadone is highly vulnerable for being abused. From 2001 to 2021, methadone abuse was one of the leading causes of overdose deaths in the United States (Merianne Rose Spencer, 2022)

Some weak opioids, such as dolantine or fortanodyn, which are 3 to 10 times less potent than morphine in analgesic efficacy (Bandieri *et al.* 2016), can also lead to severe addiction when taken for long period of time. A similar drug is codeine, which has a much weaker analgesic potency than morphine. Hydrocodone is

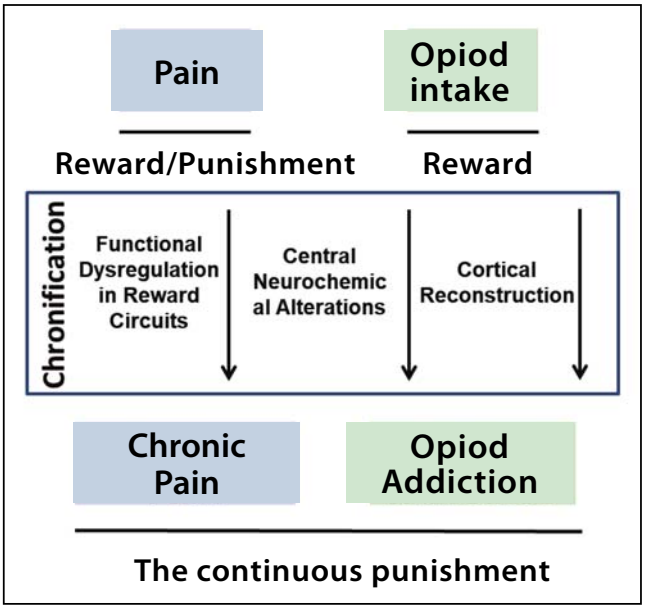

Fig. 1. The establishment of chronic pain and opioid addiction. The consolidation process of chronic pain and opioid addiction requires alteration of brain function as a result of long-term pathological impact, and will cause lasting suffering in the patient, thus being a kind of continuous punishment.

a semisynthetic codeine. As the largest market for hydrocodone, the United States had 3,274 deaths associated with hydrocodone overdose in 2014, making it the ninth leading cause of death (Warner *et al.* 2016).

Dihydroetorphine is an opioid analgesic developed in China in the late 1970s. It has a good analgesic effect, but it could also produce drug dependence under repeated usage. The abuse of dihydroetorphine is characterized by a small dosage, potent euphoric effect, short duration of action, and rapid development of tolerance. The psychological dependence of dihydroetorphine is much more severe than the physical dependence and is the major cause of dihydroetorphine addiction. These characteristics made dihydroetorphine to be frequently abused and easily overdosed (Liu *et al.* 1999).

Analgesics are also the first choice to treat opioid addiction

At present, there is a lack of drugs that are available to treat opioid addiction, especially for preventing relapse. The available drugs for relieving opioid withdrawal symptoms are also basically opioid analgesics that are inherently addictive, such as methadone or buprenorphine. These drugs are mainly working as detoxifying substances or in maintenance therapies to reduce patients' craving (for opioids). Thus avoiding the associated potential social harm.

Methadone is widely used for the detoxification of opioid addiction, and its control of withdrawal symptoms is effective and thorough (Popescu *et al.* 2014). However, when methadone is discontinued, the relapse rate can exceed 90%, thus many patients are encouraged to receive long-term maintenance therapy (Joseph *et al.* 2000a). However, methadone is also highly addictive, therefore appropriate and adequate dosage are the key factors for effective methadone maintenance treatment (Joseph *et al.* 2000). In some cases, it is necessary to determine the dosage interval of methadone for each individual to avoid the development of dependence.

When physical dependence of methadone has been established under long-term application, the symptoms of protracted withdrawal syndrome caused by cessation of methadone intake can be very severe and may include nausea, vomiting, anxiety, panic attacks, and intractable insomnia, which usually more stubborn and unbearable than the withdrawal symptoms of morphine (Joseph *et al.* 2000). These facts demonstrated that using substitutional opioids for maintenance therapy can be problematic in the long run.

Buprenorphine is a highly lipophilic drug with rapid onset of action after injection or sublingual administration (Compton *et al.* 2006). Buprenorphine is a drug with both opioid receptor agonistic and antagonist activities. Low dosage of buprenorphine administration exhibits agonistic activity on opioid receptors, while changes to antagonism when switch to high doses (Coe *et al.* 2019). Buprenorphine can effectively control and eliminate a series of withdrawal symptoms during heroin withdrawal and to some extent can also inhibit the psychological dependence of codeine. These benefits enabled buprenorphine to be an important candidate for the maintenance therapy of opioid addiction.

Buprenorphine is less addictive than methadone. Relative to methadone, withdrawal from buprenorphine requires less effort (Webster *et al.* 2020). At appropriate doses, buprenorphine is as effective as methadone in the maintenance treatment of opioid addiction. Therefore, buprenorphine could be used to replace methadone after detoxification treatment for 4 to 8 days. In addition, buprenorphine can be combinedly used with methadone or the opioid receptor antagonist naltrexone to enhance the therapeutic effects (Srivastava *et al.* 2017).

Buprenorphine sublingual tablets such as Zubsolv (buprenorphine combined with naloxone, produced by Orexo, Sweden, which is shown effective for maintenance therapy of opioid-dependent patients), are clinically applied. Compared with other buprenorphine/naloxone drugs, Zubsolv has higher bioavailability, more rapid dissolution, and smaller tablet size (Lyseng-Williamson & Katherine, 2013).

In 2016, the FDA approved Probuphine, the first implantable buprenorphine, to treat the addiction to opioids such as heroin. Porcupine is a subcutaneously implanted buprenorphine that delivers low-dose buprenorphine for up to six months with single implantation (Barnwal *et al.* 2017). Probuphine is indicated for opioid-dependent patients who have achieved a stable switch of symptoms and are being treated with low to moderate doses of buprenorphine. As compared with orally taken buprenorphine, probuphine is able

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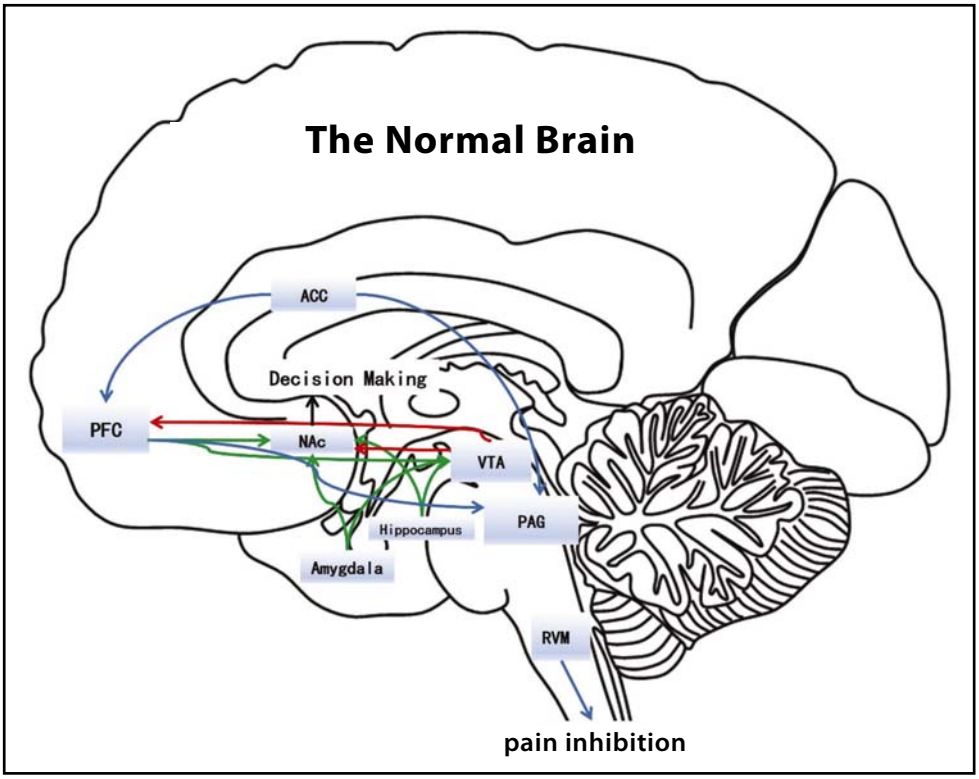

Fig. 2. Functions of the Central Reward Neuronal Networks related to Descending Pain Inhibition and Decision Making. 1) Descending pain inhibition pathway: signals are transmitted through the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) to the periaqueductal gray (PAG) and then to the rostral ventromedial medulla (RVM), where they exert direct descending pain inhibition on the spinal cord (the descending pain inhibition pathway is marked with blue arrows). 2) Decision Making pathways: glutamate from the PFC, amygdala, and hippocampus (glutamatergic pathways are marked with green lines with arrows) are transmitted to the nucleus accumbens (NAc) and ventral tegmental area (VTA) to regulate the activity of dopaminergic neurons; The VTA transmits excitatory signals to the NAc through dopamine (the dopaminergic pathway is marked with red lines with arrows). The activity of dopamine neurons in the NAc directly affects decision-making. At the same time, the VTA also transmits feedback signals to the PFC through a dopaminergic pathway. The PFC and ACC are important brain regions for reward anticipation, which are closely related to opioid addiction

to maintain more stable buprenorphine plasma concentrations and does not require additional supervision on the patient's drug intake process. This eliminates the possibility of relapse by taking inadequate buprenorphine, or the development of dependence by taking too much of it (Barnwal *et al.* 2017).

Dihydroetorphine is a widely used opioid analgesic for opioid withdrawal and detoxification in China. It has a rapid onset of action and can quickly relieve the withdrawal symptoms. The dose-decreasing applicational approach can minimize the risk of self-dependence (Wang *et al.* 1992). In the treatment of opioid withdrawal and detoxification, dihydroetorphine can be combined with methadone or buprenorphine. In most cases, better and more rapid effects can be achieved in these combinations. In addition, high patient compliance is recorded (Su *et al.* 1994; Qin *et al.* 1995). However, long-term usage of dihydroetorphine can inevitably lead to severe addiction. Thus, dihydroetorphine is not suitable for long-term maintenance therapy of opioid addiction (Ohmori & Morimoto, 2002).

Overall, the purpose of this article is to analyze and summarize the similarities and differences between opioid addiction and chronic pain from the perspective of neurobiological basis, and the relationship between hedonic drugs and analgesics, to seek breakthroughs and innovative therapeutic approaches for controlling these two types of diseases and protect human health.

THE COMMON NEUROLOGICAL BASIS FOR CHRONIC PAIN AND OPIOID ADDICTION

Commonalities between chronic pain and opioid addiction

Both pain and opioid addiction are closely related to the central reward system. Opioid intake generates euphoric sensations by directly activating the reward centers in the brain, which is usually described emotionally by patients (Elman & Borsook, 2016; Kim *et al.* 2016). On the contrary, acute pain not only generates uncomfortableness, but also produces negative emotions such as

fear and disgust. Therefore, in general, acute pain can be regarded as a punishment (as shown in Figure 1).

However in rare cases, when fear and associated negative emotions of pain are outweighed by the euphoria produced, acute pain can transform into a certain reward, that lead to self-injurious behaviors (usually as a coping mechanism for a desire to have more control over one's life). As such, it works more as a negative reinforcer by alleviating stress and anxiety (Hooley *et al.* 2020). This is because acute pain can activate the stress-relieving system, inducing the release of adrenaline and endogenous opioid substances, thereby activating the reward center in the brain (Elman & Borsook, 2016).

Pain has two natural attributes, one contributes to the intensity of pain sensation, and the other contributes to the degree of emotional unpleasantness (Liu *et al.* 2023). Distraction can reduce the intensity of pain, but usually has less effect on the emotional unpleasantness. While a good mood can improve the pain associated unpleasantness, but does not necessarily reduce the sensory intensity of pain.

Normally, the negative emotions induced by pain can be counteracted by rewards. For example, monetary compensation can reduce the pain associated sensory intensity and emotional unpleasantness in tested subjects. Conversely, additional negative emotions can increase the overall intensity of the perception of pain (Bushnell *et al.* 2013). Extreme unpleasant feeling such as loss of loved ones is often described as heartache, indicating that a negative psychological states and pain may share common neurobiological mechanisms (Strigo *et al.* 2008). Similarly, for some patients the main motivation of opioid abuse is to tackle the painful life experiences, by neutralizing negative emotions through immersing in the euphoria produced by opioids (Loganathan, 2021).

In majority of cases, acute pain (usually after damage or surgery) will not develop into chronic pain if it is cured in time. Similarly, occasional medical use of opioids does not necessarily lead to addiction. It is a gradual process for acute pain to become chronified (Liu *et al.* 2023). So is the development of opioid addiction, which requires reinforcement from repeated hedonic usage of drugs over a substantial period of time, to establish physical and more importantly psychological dependence (Gardner, 2011). In the process of occasional pain or opioid use evolving into chronic pain or opioid addiction, neurochemical and functional changes of the CNS played an important role (Kelley, 2004; Bushnell *et al.* 2013; Elman & Borsook, 2016) (Figure 1).

Both chronic pain and drug addiction can cause functional impairments in the brain. Chronic pain causes lesions in both gray and white matter, accompanied by a decline in the overall health status of the white matter (Bushnell *et al.* 2013). The abuse of addictive substances, such as heroin, MDMA, and alcohol, can also cause sustained and irreversible functional damage in brain (Mccann *et al.* 1998; Andersen & Skullerud, 1999). Compared with healthy subjects, patients with chronic pain or opioid addiction showed a significant reduction of neuronal activity in certain brain regions, such as in the central reward system or in the brain regions associated with the descending inhibition of pain (Tzschentke & Schmidt, 2003; Bushnell *et al.* 2013), indicating the occurrence of neurochemical changes in these two types of patients.

After taking drugs for the first time, users usually experience feelings of euphoria, novelty, or even tension, but do not immediately become addicted. The formation of psychological dependence requires the involvement of memory and learning (Kelley, 2004; Gardner, 2011). One precondition of drug addiction is that abusers must have the strong expectation / craving for drug intake. When an individual has the psychological expectation of taking a drug, and is eventually satisfied by successful drug intake, the euphoria could be further enhanced with the sense of achievement (of satisfying one's desire), resulting in the positive reinforcement of learning. On the contrary, accidental passive usage of a drug (e.g., for one time) without awareness usually do not induce psychological craving and associated addictive behaviors (Kelley, 2004). However, repeated opioid consumption even without awareness is problematic, which will result in serious physical dependance and withdrawal syndromes when discontinued.

Expectations can also affect the sensitivity of pain. For example, the positive expectation (that pain will be relieved in a short time) can produce a placebo effect to induce analgesia, while negative expectations can completely reverse the efficacy of analgesics at clinical effective dosages, and thus result in a nocebo effect (Elman & Borsook, 2016). Furthermore, the patient's persistent negative expectations may accelerate the solidification of chronic pain.

The establishment of psychological dependence on exogenous opioids usually stems from the expectation of recreational effects produced by these drugs. These effects are usually being regarded as the best solution life problems of patients with opioid use disorder (OUD). And once the habit of opioid abuse is consolidated, substance dependence will be more difficult to quit (Jamison & Mao, 2015).

Once chronic pain is established, the patient could be suffered from consistent pain and spontaneous pain, which leads to mental weakness, inability to concentrate, and may therefore become more dependent on medication by the relieving drugs (Vowles *et al.* 2015). Correspondingly, the reward neuronal network of OUD patients becomes dysfunctional after the long-term abuse of opioids. The autonomous inhibition of endogenous opioid synthesis may result in anhedonia (Mitsi & Zachariou, 2016).

As the body develops resistance and tolerance to exogenous opioids, a much larger doses are required

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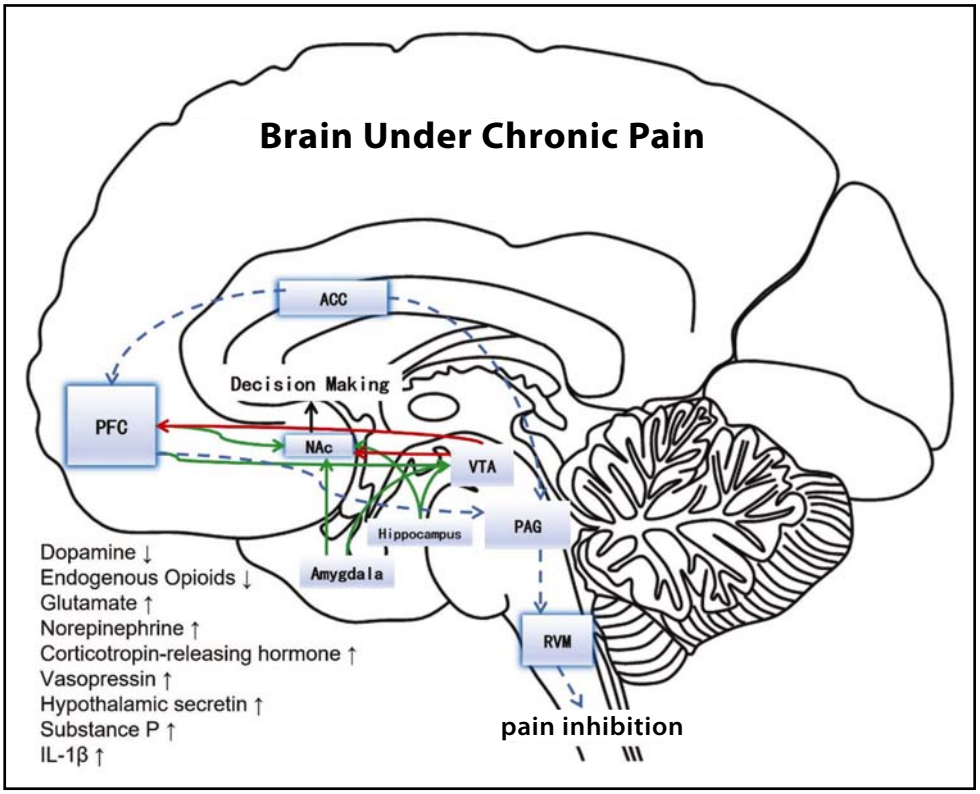

Fig. 3. Abnormalities in descending pain inhibition in the brain under chronic pain conditions. Signal transmission was decreased from the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) to the periaqueductal gray (PAG), and from the PAG to the rostral ventromedial medulla (RVM, indicated by dashed blue lines). The PFC, ACC, VTA, and NAc showed decreased endogenous opioid secretion and dopamine activity (blue light). " Chronic pain has changed cellular metabolism of neurons, with decreased secretion of dopamine and endogenous opioid peptides (marked by "↓"annotation) and increased production of glutamate, norepinephrine, corticotropin-releasing hormone, vasopressin, hypocretin, substance P, and interleukin-1β (marked by "↑" annotation).

to generate the same degree of euphoria that dramatically increases the related adverse events and produces serious withdrawal symptoms when stop using these drugs (Qian *et al.* 2005).

Patients with severe opioid dependence are basically in a state of daily panic and normally have lost their working abilities. In addition, the inability to cure chronic pain or to quit drug addiction will also result in self-abandonment and disgust, which will further lead to increased incidences of major depression (Tzschentke & Schmidt, 2003). Therefore, the consolidation of chronic pain and drug addiction will cause lasting suffering in the patient, like a certain kind of continuous punishment (Figure 1).

The reward pathways related to chronic pain and opioid addiction in normal brain

The specific function of the human brain is achieved by connecting neurons in different brain regions through electrical signals to exchange and process information. The neurons in each brain region have different properties and have participated in the generation of functions such as cognition, memory, and decision making (Raichle & Mintun, 2006).

In the normal brain, the reward neuronal pathways are comprised of multiple brain regions that are closely related to function of decision making that are essential to the life and survival (Figure 2). In addition, the human reward neuronal pathways are closely related to chronic pain and drug addiction (Cooper *et al.* 2017). The brain regions involved in this pathway include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala, hippocampus, ventral tegmental area (VTA), and nucleus accumbens (NAc) (Bushnell *et al.* 2013; Elman & Borsook, 2016). The human PFC and ACC are associated with anticipation, the hippocampus is mainly involved in memory formation, and the amygdala is an emotional center that controls emotions such as fear and intense craving (Cooper *et al.* 2017; Murray *et al.* 2017; Solinas *et al.* 2019).

Dopamine neurons are concentrated in VTA and NAc. The sustained release of dopamine in these areas can produce feelings of euphoria and satisfaction, therefore is the core part of the human brain's motivation and reward center (Cooper *et al.* 2017; Yang *et al.* 2018; Solinas *et al.* 2019). The PFC, amygdala, and hippocampus are involved in the regulation of neural activity in VTA and NAc through the excitatory neurotransmitter glutamate (Yang & Wang, 2017). While, in VTA, signals are transmitted to NAc and PFC via dopamine (Volkow & Morales, 2015; Solinas *et al.* 2019) (Figure 2). These three dopamine-associated brain regions play a crucial role in human decision-making, especially the activity of dopamine neurons in the NAc is closely associated with immediate decision-making (Tzschentke & Schmidt, 2003; Solinas *et al.* 2019).

The reward center of the human brain integrates functional regions of expectation, emotion, memory, and enjoyment of instant euphoria. These brain regions communicate efficiently with each other, enabling people to perform tasks such as cognition and learning,

that are important for adaption to the environment and expand personal ability (Gardner, 2011; Lewis *et al.* 2021). The reward center is also positively associated with positive emotions such as confidence and self-esteem. Disfunction of the reward system can generate a deficit of positive emotions in patients with chronic pain or drug addiction, which is one of the reasons that leads to the low quality of life in these people (Tzschentke & Schmidt, 2003; Elman & Borsook, 2016).

The reward pathway in the human brain is also partially overlapped with the neuronal circuit associated with the descending inhibition of pain, and PFC played important roles in both systems (Chau *et al.* 2018). Descending pain inhibition is initiated in the anterior cingulate cortex (ACC) and the PFC, both of which act on the periaqueductal gray (PAG), and then relay electric signals to the rostral ventromedial medulla (RVM) in the brainstem to directly suppress the ascending pain signaling (Kelley, 2004). (Figure 2)

Chronic pain induced key changes in central neuronal networks

Under normal conditions, the descending pain inhibition pathway can effectively suppress the ascending pain signals coming from the spinal cord. However, in the state of chronic pain, this endogenous analgesic system is impaired, with a reduction of neural activity to be observed in the ACC, PFC, and RVM (Figure 3), contributing to the establishment persistence of pain (2013).

Opioids are particularly potent analgesics. PFC, PAG, RVM, and spinal cord are targeted organs of opioids. Chronic pain results in a reduction in endogenous opioid production and a corresponding reduction in dopamine levels in these regions, which ultimately causes the loss of function in neural circuits responsible for spontaneous inhibition of pain (Serafini *et al.* 2020) (Figure 3).

In particular, reduced endogenous opioids and dopamine signaling in the PFC can cause anhedonia and depression in patients with chronic pain (Bair *et al.* 2003; Tzschentke & Schmidt, 2003; Elman & Borsook, 2016). The production of placebo analgesia in human due to the positive anticipation also depends on the involvement of endogenous opioids and their receptors in PFC and ACC (Petrovic *et al.* 2002; Elman & Borsook, 2016). Intriguingly, the generation of spiritual powers such as faith and belief may also relate to the endogenous opioid system, suggesting that strong belief can affect the perception of pain, while persistent pain can weaken patients' positive attitude and mental strength (Elman & Borsook, 2016).

Disruption of the normal activity of the glutamate system is another characteristic of chronic pain. Findings using proton magnetic resonance spectroscopy have revealed increased glutamate concentrations in frontal cortical regions in patients with chronic back pain (Tzschentke & Schmidt, 2003).

Fibromyalgia is associated with deficits in intracortical modulation involving glutamatergic mechanisms. In patients with fibromyalgia, a significant reduction of both intracortical facilitation and inhibition was observed following application of transcranial magnetic stimulation (TMS), which was thought to be helpful to restore the balance of the excitatory and inhibitory neurotransmission (Mhalla *et al.* 2010).

Patients with fibromyalgia were also shown to have deficits in working memory and emotional decision-making (Tzschentke & Schmidt, 2003). In accordance, animal studies also demonstrated that chronic pain-induced feedforward inhibition of the basolateral amygdala (BLA) in the medial prefrontal cortex that impairs decision-making abilities (Yang *et al.* 2017).

In addition to the reduction of the synthesis of endogenous opioids and their affinity to related receptors, and the disturbance of neurotransmitter transmission (mainly dopamine and glutamate), chronic pain and drug addiction also cause long-term changes in the metabolism of nerve cells in the CNS, leading to excessive production of stress hormones such as norepinephrine, corticotropin-releasing hormone, vasopressin, and hypocretin, as well as the pro-inflammatory substances such as substance P and interleukin-1β, which can cause local inflammation (Del Rey *et al.* 2011; Elman & Borsook, 2016).

Opioid addiction induced functional changes in key neuronal pathways

Endogenous opioids are not only key to the perception of pleasure, but also crucial for maintaining the hemostasis of neurotransmitters in CNS. When patients are in the state of opioid addiction, key functions of the brain are affected under the long-term impact of drugs (Figure 4). In particular, the secretion of endogenous opioid peptides in the PFC, VTA, and NAc are reduced, resulting in further reduction of dopamine activity in these regions, and rendering patients prone to develop anhedonia (Solinas *et al.* 2019). In situations that patients are tempted by the hedonic effects induced by opioid intake, glutamatergic activity in the PFC, amygdala, and hippocampus is increased. Such an increase in glutamate neurotransmission subsequently activates dopaminergic neurons in the VTA and NAc. The sustained activation of dopaminergic neurons in the NAc and ventral striatum will directly lead to the behaviors of compulsive drug seeking and relapse (Tzschentke & Schmidt, 2003).

The relapse of opioid dependence is the most difficult problem for drug rehabilitation. Opioids can produce strong physical dependence, while some other drugs, such as cocaine, cannabinoids, and LSD, produce only weak physical dependence. However, even in different type of drugs, the mechanism of relapse is highly consistent. The disturbance of dopaminergic and glutamatergic neurotransmission in the reward center of brain is the direct cause of relapse. Experiments of animal

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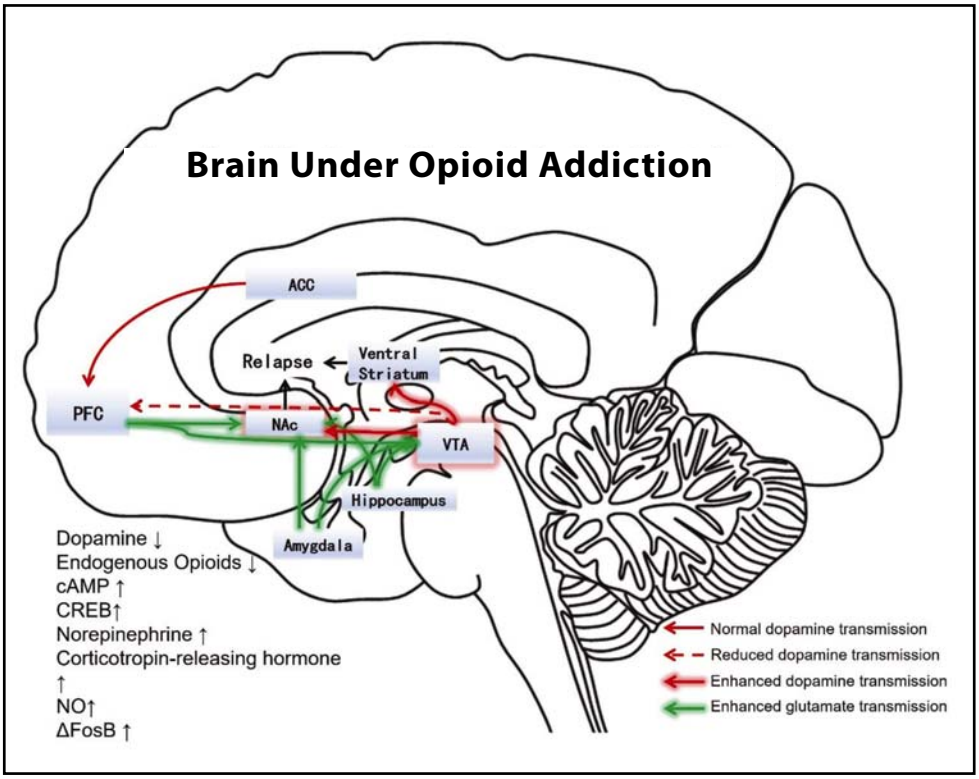

Fig. 4. Abnormalities in brain function under conditions of opioid addiction. 1) Under the normal state of opioid addiction but without drug intake, the prefrontal cortex (PFC), amygdala, and hippocampus showed insufficient endogenous opioid production and decreased dopamine levels. 2) Under the temptation of opioid intake, there were increased glutamatergic inputs from the PFC, amygdala, and hippocampus to the nucleus accumbens (NAc) and ventral tegmental area (VTA) (illustrated with strong green lines), which resulted in increased activity of dopaminergic neurons in the NAc and VTA (illustrated with strong red lines); There are also increased excitatory dopaminergic signals from the VTA to the NAc (illustrated with strong red lines) and decreased dopaminergic feedback signals to the PFC (dashed red lines), which may be one of the causes for the decreased behavioral control by the PFC. Contrary to the normal condition, not only the activity of dopamine neurons in the NAc, but also the related dopamine neurons in the ventral striatum are directly involved in the compulsive drug use. 3) Abnormal cellular metabolism in the opioid-addicted brains: decreased secretion of dopamine and endogenous opioid peptides (marked by "↓") and increased release of, cAMP, CREB, norepinephrine, corticotrophin-releasing hormone, nitric oxide (NO) and ΔFosB (marked by "↑"), accompanied by phasic release of dopamine and glutamate

studies have shown that microinjection of dopamine into the NAc could induce drug craving, while injection of glutamate AMPA receptor inhibitors into the same region suppressed such compulsive craving for drugs (Cornish & Kalivas, 2000; Tzschentke & Schmidt, 2003).

The PFC also plays a critical role in drug relapse. For example, local inactivation of the medial PFC can completely block the conditioned drug-seeking behavior induced by cocaine cues in animals, which may relate to the disruption of the expectation of drug associated pleasure (Franklin & Druhan, 2000; Kelley, 2004). In addition to drug relapse, the PFC and NAc are also involved in motivation, learning, decision making, and goal associated reward. When this system is damaged in patients with opioid addiction, the signal output for behavior control from the NAc is gradually replaced by other parts of the ventral striatum, leading to more compulsive behaviors (Figure 4). Such damage not only decreases the abilities required to adapt to the environment and return to society, but also diminishes pleasure in daily life, resulting in the deprivation of self-awareness and self-esteem (Tzschentke & Schmidt, 2003; Everitt *et al.* 2008).

In addition, cellular metabolism of the brain is also disrupted in opioid addicts. In these patients, the increased expression of cyclic adenosine monophosphate (cAMP) and response element binding protein (CREB), especially in the NAc, leads to the decrease of dopamine activity in the reward center, accompanied by the increased expression of ΔFosB, that alters the signal transduction between neurons, to an increase their sensitivity in response to opioids. Furthermore, increased secretion of norepinephrine, corticotropin-releasing hormone, and nitric oxide has contributed to the promotion of drug-seeking behavior (Elman & Borsook, 2016) (Figure 4).

INNOVATIVE PHARMACOLOGICAL APPROACHES FOR THE TREATMENT OF CHRONIC PAIN AND OPIOID ADDICTION

At present, the management of opioid addiction mainly consists of detoxification, complete withdrawal from opioids to accomplish abstinence, returning to the society, and relapse prevention. At present, there are effective methods for detoxification and complete withdrawal. However, after returning to society, most opioid addicted patients relapsed within half a year (Qin *et al.* 1999). Thus, prevention of relapse is the key for the successful rehabilitation from opioid abuse. Similarly, the treatment of intractable chronic pain is also a great clinical challenge. The lack of effective non-opioid analgesics is one of the important reasons for the widespread abuse of opioids in patient (Schug *et al.* 2003).

There are many similarities between the mechanisms of opioid abuse, relapse and chronic pain. Based on these similarities, here we have discussed the current available and potentially effective pharmacological therapies as an innovative approach.

Current available drug therapies for relapse of opioid abuse

Naltrexone / naloxone is the only widely used drug for the prevention of relapse after opioid detoxification, which can reduce the euphoric feeling of drugs by antagonizing opioid receptors. However, it cannot reduce the temptation or increase the motivation of patients to stay in abstinent. Therefore, the effect disappears after stop taking the drug. Therefore the patient's psychological dependences on the opioids cannot be cured by naltrexone / naloxone (Adi *et al.* 2007).

The development of vaccines, which generate antibodies to neutralize opioids in the blood and inactivate them, is a new concept for relapse prevention (Kelly, 2017). However, because opioids and other types of drugs can be substituted for each other, and one vaccine cannot be effective against all targets, especially for those with small molecular weights (that cannot be recognized by the body's immune system). Like naltrexone / naloxone therapy, vaccines cannot completely eradicate the psychological dependence. Thus, the effectiveness of such approach for preventing relapse needs further confirmation (Bloom & Bushell, 2022).

Due to the failure of anti-relapse approach using non-addictive drugs, other opioids (such as methadone and buprenorphine) are widely applied to replace the abused ones even after the successful withdrawal, as the long-term maintenance therapy to prevent relapse (Bell & Strang, 2020). However, in essence, opioid maintenance therapy is still the substitution of one poison for another, and cannot truly help the patients get rid of psychological dependence. Similarly, many patients with chronic pain also become drug dependent due to abuse of opioid analgesics. Therefore, there is an increasing urgency to develop innovative non-opioid drugs to treat these two clinical conditions.

Recent studies have indicated that some non-opioid analgesics, especially those who are effective for chronic pain, also exhibit promising effects to inhibit drug craving, including drugs that can modulate the neurotransmission of dopamine, glutamate, and γ-aminobutyric acid (GABA), as well as Chinese herbal medicines and their active extracts (Table 2). Because these drugs are generally non-addictive, so that they can be applied safely for long-term, providing new options for maintenance therapy, and to prevent the relapse of opioid dependence.

Drugs modulating dopaminergic neuroactivity

Affected by the long-term use of opioids, normally the production of endogenous opioids and dopaminergic neuronal activity are disrupted in the brain of opioid addicts. Meanwhile, the insufficient dopaminergic neuronal activity in the limbic system is also an inherent characteristic of patients with chronic pain (Volkow *et al.* 2019; Wise & Jordan, 2021). Therefore, drugs that modulate dopaminergic neural activity may have modulatory effects on both symptoms (Table 2).

Dopamine D2 and D3 receptors are highly associated with the reward mechanism in the limbic system. Dysfunction of D2 receptors leads to compulsive cravings for substances such as alcohol, drugs, tobacco, and food and compulsive behaviors such as pathological gambling (Blum *et al.* 1996). While, the activation of dopamine D3 receptors helps to alleviate the anhedonia and compulsive drug seeking during withdrawal (Elman & Borsook, 2016).

Dopamine D2 and D3 receptors are also highly associated with central mechanisms of pain. It has been demonstrated by positron emission tomography (PET) that D2/3 mediates placebo analgesia (Qiu *et al.* 2009), and loss of the function of D3 receptors abrogates the analgesic effect of morphine in the spinal cord (Brewer *et al.* 2014). The examples highlight the potential use of D2- or D3-receptor agonists, such as lisuride, bromocriptine, pramipexole, and quinpirol, to treat chronic pain and prevent the relapse of opioids.

In addition, drugs that can indirectly increase the concentration of dopamine in the intracellular space of the CNS by inhibiting its metabolism, such as catechol-O-methyltransferase (COMT) inhibitors and monoamine oxidase inhibitors (such as pirindole), have been shown to be effective against chronic pain (Tort *et al.* 2012; Elman and Borsook, 2016). The combination of COMT and dopamine precursors also alleviated compulsive drug seeking in patients with opioid addiction (Elman & Borsook, 2016). However, further studies are still needed to confirm whether monoamine oxidase inhibitors can be used for the prevention of opioid relapse.

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Drugs modulating the glutamatergic neuronal activity

In addition to reduced endogenous opioid production, hyper-glutamatergic neuronal activity in the limbic system is a common mechanism of chronic pain and opioid craving. Therefore, inhibition of the overactive glutamatergic neural pathway may have therapeutic potential. In such regard, antagonists of glutamate receptors could be used (Table 2).

However, potent antagonists of NMDA receptors (e.g., zocilpine), tend to have the opposite effects and cause relapse, whereas weak antagonists of NMDA (e.g., dexmedetomidine, acamprosate, and dextromethorphan) may prevent relapse (Tzschentke & Schmidt, 2003). Among them, dextromethorphan has been reported to reduce the physical withdrawal symptoms of opiates, especially in heroin addicts. Dextromethorphan also has analgesic effects on chronic pain and strong antitussive effects (Koyuncuoglu & Saydam, 1990).

AMPA receptor is another glutamate ion channel receptor in addition to the NMDA receptor. Modulators of AMPA receptors possess a large potential as a therapeutic agent for opioid relapse. In animal experiments, AMPA receptor antagonists and allosteric modulators have shown to be effective in inhibiting conditioned place preference and drug-seeking behaviors (Bauer *et al.* 2022). At present, there is a selective AMAP receptor antagonist (YM-872) in the clinical development stage for the treatment of ischemic stroke, but whether this drug can be used for preventing opioid relapse needs further verification (Tzschentke & Schmidt, 2003).

In addition to ion channel receptors, glutamate also has a class of G protein-coupled receptors, among which the mGluR5 receptor is revealed to be involved in pain and addiction. mGluR5 knockout has been shown to reduce the drug craving in animals (Chiamulera *et al.* 2001; Tzschentke & Schmidt, 2003) and blockade of the mGluR5 pathway in the central nervous system can reduce nerve injury-induced chronic pain, which provides a theoretical basis for the development of new mGluR5 receptor antagonists for the treatment of opioid addiction and chronic pain (Vincent *et al.* 2016).

Another G-protein-coupled receptor for glutamate, mGluR7, has been implicated in substance dependence. Systemic administration of the mGluR7 receptor antagonist, AMN082, or microinjection of AMN082 into the cortico-limbic system reduced cocaine and nicotine compulsive seeking behaviors in animals (Li & Markou, 2015), making AMN082 a potential candidate to be used for the treatment of opioid addiction and relapse prevention.

Drugs that modulate the GABAergic neuroactivity

GABA is an inhibitory neurotransmitter. Because hyperexcitability of glutamatergic neurotransmission in the limbic system is a common biological basis for both chronic pain or opioid addiction, neutralizing such glutamate toxicity by drugs that enhance GABA neuroinhibitory activity can be one of the possible interventions for these two disorders (Table 2).

Drugs in this group include derivatives of GABA, gabapentin, and pregabalin. They exhibit antiepileptic effects and have been used as first-line drugs for the treatment of chronic pain, especially for neuropathic pain (Gilron *et al.* 2015). Gabapentin has also been used to treat substance dependence. In animal experiments, gabapentin reduces the free intake of abused substances in addicted rats, providing the possibility of the potential use of gabapentin in clinical practice to reduce the psychological drug craving (Koob, 2010).

Effective ingredients from traditional Chinese medicine

Traditional Chinese medicine (TCM) plays an important role in the treatment of chronic pain and the prevention of opioid relapse due to their non-addictive nature and can be purchased directly in pharmacies with a prescription (Jiang *et al.* 2022).

At present, the active ingredients from TCM that have been thoroughly studied for detoxification of opioids mainly include *Corydalis yanhusuo*, *ginseng*, *Astragalus mongholicus*, and *Salvia miltiorrhiza*, etc. (Xia *et al.* 2016) (Table 2).

Corydalis yanhusuo has the effect of promoting blood circulation, nourishing "qi" and relieving pain. Modern studies have shown that it has good sedative and hypnotic effects and ameliorates chronic pain. L-tetrahydropalmatine and de-hydrocorydaline have been identified from *Corydalis yanhusuo* to be its active ingredients. Tetrahydropalmatine is an active constituent of herbal preparations containing plant species of the *genera Stephania* and *Corydalis*. It is a non-addictive agent with analgesic and sedative effects (Xia *et al.* 2016; Gong *et al.* 2016).

This alkaloid extracted from TCM were found to be able to inhibit conditioned cue-induced heroin and methamphetamine relapse in rats, by inhibition of dopaminergic neurotransmission in the brain. Dehydrocorydaline is an alkaloidal component isolated from *Rhizoma corydalis*, and has been shown to relieve both acute and chronic pain, by acting through receptors other than the opioid receptors, most likely by binding to the dopamine receptor D2 (Zhang *et al.* 2014).

INNOVATIVE APPROACHES OTHER THAN DRUG THERAPY FOR THE TREATMENT OF CHRONIC PAIN AND OPIOID ADDICTION

Medical device

In addition to drug therapy, the application of medical devices to noninvasively regulate cortical neuronal activity through electric or magnetic fields and restore normal cortical function is another effective method

Tab. 2. Pharmacological treatments that potentially effective in chronic pain and opioid addiction

Type of Drugs	Opioid Addiction	Chronic Pain
Drugs modulating dopaminergic neurotransmission	• Dopamine receptor D2 or D3 agonists: lisuride, bromocriptine, pramipexole, • Catechol-O-methyltransferase inhibitors	• Dopamine receptor D2 or D3 agonists:quinpirol, bromocriptine, pramipexole • Catechol-O-methyltransferase inhibitors • Monoamine oxidase inhibitor: pirlindole
Drugs modulating glutamatergic neurotransmission	• Weak NMDA antagonist: Memantine, dextromethorphan, acamprosate • AMPA antagonist: YM-872 • mGluR5 antagonist • mGluR7 agonist: AMN082	• Weak NMDA antagonist: dextromethorphan • mGluR5 antagonist
Drugs modulating GABAergic neurotransmission	• Gabapentin	• Gabapentin • Pregabalin
Herbs / extracts from TCM	• TCM Herbs: Corydalis yanhusuo, ginseng, Astragalus mongholicus, Salvia miltiorrhiza • TCM Extracts: tetrahydropalmatine, dehydrocorydaline	• TCM Herbs: *Corydalis yanhusuo* • TCM Extracts: Ligustrazine, tetrahydropalmatine

to treat addiction and chronic pain. Such treatments include transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), that are applied using medical devices.

tDCS consisted of two surface electrodes, an anode and a cathode, that applies a weakly polarized direct current to the cerebral cortex. When tDCS was started, the excitability of the cortex adjacent to the anode was increased, while the neurons in cortex adjacent to the cathode was inhibited and became more difficult to generate action potentials (Lupi *et al.* 2017; Gallucci *et al.* 2019; Young *et al.* 2020).

Membrane polarization is the main mechanism of the immediate effect of tDCS, while the prolonged effect is related to its regulatory effect on neural synaptic plasticity (Nakamura-Palacios *et al.* 2016; Lupi *et al.* 2017; Young *et al.* 2020). tDCS treatment can alleviate the dysfunction of the dorsolateral prefrontal cortex (DLPFC), which plays an important role in the descending pain inhibition and the reward system (Lefaucheur *et al.* 2017).

Repetitive transcranial magnetic stimulation (rTMS) can use magnetic fields to induce electric fields and precisely stimulate the cortex through navigation systems (such as the NBS system from Nexstim, Finland), with different frequencies to achieve therapeutic purposes. The high frequency stimulation (>1Hz) of the cortex produces excitation, whereas stimulation at low frequencies (≤1Hz) can inhibit the firing of neurons. Because of its pain-free and non-traumatic features, it is now used as an advanced tool for therapy of a variety of neurological disorders, and to explore the function of the human cerebral cortex (Lupi *et al.* 2017).

Activation of DLPFC by rTMS can prevent addicted patients from craving drugs such as nicotine and cocaine (Gorelick *et al.* 2014). In addition, stimulation of the DLPFC or the primary motor cortex (M1) by rTMS can effectively relieve chronic pain such as neuropathic pain, phantom pain, and fibromyalgia without observed side effects (Goudra *et al.* 2017). Treatment of pain and addiction by tDCS and rTMS can improve the function of DLPFC by regulating / synchronizing the neural activities, which can also lead to the alleviation of depressive symptoms, thus there is an additional benefit for patients with chronic pain or drug addiction who also have depression (Avissar *et al.* 2017; Lefaucheur *et al.* 2017).

Another device that can be used for the treatment of drug addiction and chronic pain is Han's acupoint nerve stimulator (HANS) developed by Jisheng Han in China, which applies the principle that acupuncture or electrode transcutaneous stimulation can facilitate the production of endogenous opioid. This device releases low frequency electric signals (2/s) and high frequency signals (100/s) for electrical stimulation, causing nerve endings to secrete different kinds of endogenous opioids such as enkephalins and endorphins, in various parts of the brain, so as to greatly relieve symptoms of opioid withdrawal (including emotional irritability, tachycardia, insomnia, loss of appetite etc.), and even psychological drug craving patients with opioid addiction.

Behavioral and psychological therapy

Chronic pain and drug addiction are often associated with depression and personality distortion. Therefore, in these two clinical situations, it is not enough to only focus on the elimination of acute physiological symptoms. Psychological issues should not be neglected, and assistance in this regard can be highly beneficial to a large group of patient population (Sheng *et al.* 2017; Zis *et al.* 2017). Especially after receiving the treatment of the drug and medical devices, when

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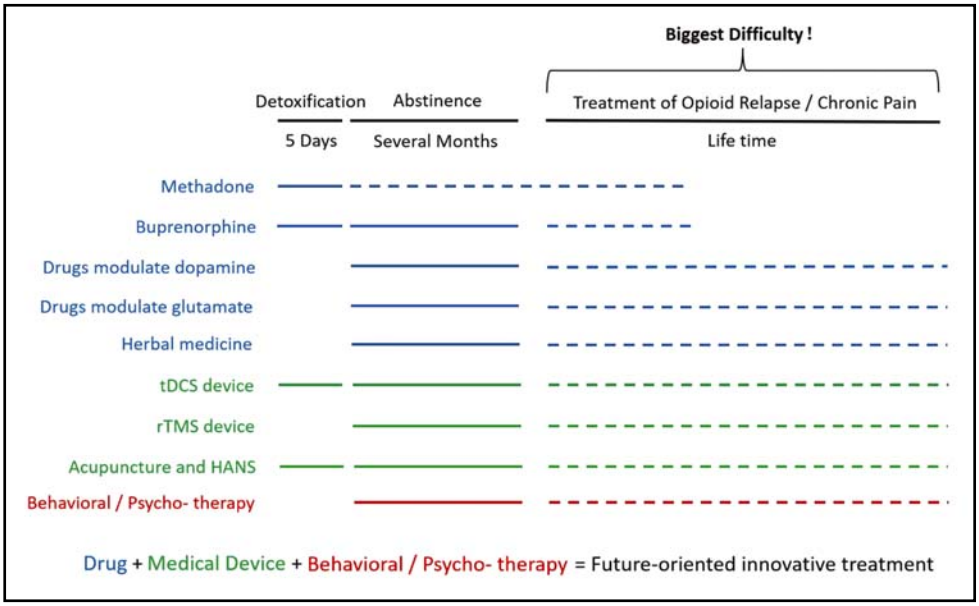

Fig. 5. Targeted combined therapeutic system for the treatment of opioid addiction and chronic pain. Drug therapy is marked in blue; medical device therapy is marked in green; psychotherapy is marked in red. The solid line represents the programmed treatment plan; the dashed line represents the maintenance regimen administered regularly or irregularly as needed. Methadone and buprenorphine are associated with the side effects of opioids, and not suitable to be used in a long-period maintenance plan, so that the length of the dash line is reduced compared with other therapies.

the patient's brain function and abilities in self-control and decision-making are improved, adding in psychological assistance / therapy may produce more comprehensive effects (Fisher *et al.* 2018; Cohen *et al.* 2021).

Rebuilding of confidence (to have strong self-belief) is the most imperative thing in patients with pessimism after early stages of unsatisfactory treatment that leads to decreased ability for social adaptation (Batty *et al.* 2020). In addition, through psychological therapy, it is important to help the patients (in a way that they can readily accept) to reestablish the right concept of values, strengthen their power of will reshape their personality, and gradually guide them to identify advantages and disadvantages, until their ability to make the correct choice is regained, to eventually get rid of the negative psychological impact induced by opioid abuse or chronic pain (Fisher *et al.* 2018). In addition, receiving follow-up treatments provided by professionals, encouraging patients to interact with their family members, and engaging in positive social activities may improve psychological recovery and ultimately speed up the return to society (Batty, *et al.* 2020).

SUMMARY

Opioid addiction and chronic pain are very difficult to be cured and seriously threaten human health in general. Both diseases have a shared basis of pathology in the limbic system of the brain, in which dopaminergic, glutamatergic, GABAergic systems, and endogenous opioid systems are deeply involved. As for the therapeutic strategies, the effect of current medication is unsatisfactory and associated with uncertainties and even strong side effects, especially for the long-term usage of opioid drugs. While most of above-described non-opioid analgesics (drugs that potentially used for detoxification and maintenance therapy for opioid addiction), medical devices and behavioral / psychological therapies, are still in the stage of exploration or under development, so that their effects need to be verified.

In addition, most of the therapies that have been successfully applied in the clinic are usually used alone. However, as drugs, medical devices, and behavioral / psychological treatments are different in their mechanisms of action. They may mutually reinforce each other when combinedly used. In particular, the behavioral therapy that mainly focused on shaping heathy habits using motivational approaches, and psychological therapy that aiming to regain the ability for emotion control can generate synergy to improve the therapeutic effects of co-applied drugs (Figure 5).

Opioidergic drugs such as methadone and buprenorphine are not suitable to be used in a long-period maintenance plan, but herbal medicines, medical devices, and behavioral / psychological therapies can be used for the maintenance strategy that lasts over a life time. Therefore, in the journey of mankind to fight against drug addiction and chronic pain, if we can find a rich arsenal of new drugs and use them in combination with medical devices and behavioral / psychological approaches, to create a targeted combined therapeutic scheme (Figure 5); maybe we can find a new way to defeat these two diseases, and protect human health and social harmony.

This combined therapeutic scheme consists of medications that are mechanistically different but supplementary to each other. In addition, the duration of action of each type of therapy is also complementary. The net effect of such combination may result in an integrative synergy, leading to a better treatment outcome according to the stage of disease progression.

AUTHOR CONTRIBUTIONS

Han C.-J., Zhen S., Li T., and Tang M. are co-first authors; All authors were involved in preparing the manuscript; All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors declare that there is no competing interest.

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