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Chapter

Present and Future Pharmacological Treatments for Opioid Addiction

Maria Carmen Blanco-Gandía, Sandra Montagud-Romero and Marta Rodríguez-Arias

Abstract

When treating opioid addiction, multidisciplinary treatment is highly recommended, but pharmacotherapy plays a key role. Although the ideal goal is to achieve complete abstinence, an elevated percentage of opioid addicts requires maintenance substitution therapy. In the first section of this chapter, we will focus on the current pharmacological interventions to treat opioid addiction, such as methadone, buprenorphine, and naltrexone. Thanks to these medications, people are able to go back to their normal lives, by preventing withdrawal symptoms, reducing craving, and increasing their adherence to psychotherapy. In the second section, based on the evidence that addiction induces neuroadaptive changes in several neurotransmission systems, we focus on the wide range of possible pharmacological developments at the preclinical and clinical levels, which in recent years have increased considerably.

Keywords: opioid, methadone, buprenorphine, naltrexone, naloxone

1. Introduction

Addiction is a chronic and multifactorial disorder characterized by compulsive drug seeking and use, despite its harmful consequences. Chronic opioid use induces profound molecular and behavioral changes, inducing long-lasting changes in brain plasticity [1]. During the use of the drug, reward and motivation circuits are modified, and new learning and memories are created in relation to the pleasurable effects of the drug and the context in which it is consumed [2]. These memories will later be responsible for the vulnerability to relapse even after a long period of withdrawal. In order to restructure these memories and avoid relapse and craving to opioids, the first recommended approach currently consists in combining psychotherapy with pharmacological substitution therapy [3]. Opioid addiction is currently a major medical and social problem, and its abuse and recreational use have been declared an epidemic in the USA [4, 5], with more than 90 people dying from an opioid overdose every day [6].

Opioids are highly addictive because they induce euphoria (positive reinforcement) and the cessation of a chronic use produces dysphoria [7]. The non-medical opioid use is a major public health challenge, making opioids the second most used illicit drug in the USA [8].

The use of opioids has increased 10- to 14-fold in the last 20 years, including those taken under supervision and recreational use [9].

In relation to this, opioids are one of the most commonly misused medications. Although it is usually prescribed to treat pain, its abuse has serious medical consequences. According to NIDA (National Institute on Drug Abuse, NIH), misuse of prescription drugs is defined as taking a medication in a manner or dose different than has been prescribed, either for a medical complaint, such as pain, or to feel euphoria [2]. The number of opioid prescriptions has increased significantly since the early 1990s [10], with this easier access to the drug being one of the reasons for the high prevalence of opioid misuse [9]. However, other factors can contribute to the problem, such as the lack of information about the addictive properties of prescription opioids, which are perceived as less harmful than illicit opioids [11, 12]. Regardless of the primary causes, there has been a dramatic increase in the number of treatment admissions for addictive disorders related to prescription opioids, as well as the associated overdose deaths in the past 15 years [8, 13, 14].

Pharmacological treatments are essential for initiating and sustaining effective patient-, public health, and system-level interventions to reduce opioid-related morbidity and mortality [15]. In the specific case of opioid use disorders, pharmacotherapy is strongly recommended as a part of an integrated approach, also including psychosocial interventions, psychotherapy, or relapse prevention programs [16]. Until the 1960s, the opioid addiction treatment was only oriented towards abstinence, but then the potential action of methadone as a maintenance treatment for opioid addiction was evaluated [17]. Currently, although complete abstinence continues to be the best possible outcome, the most common option is life-long substitution therapy. While the currently approved medications improve the outcomes, relapse rates are still high, and pharmacotherapy is not effective in all patients [18].

The final goal of the treatment is to reduce the risk of illicit opioid use, overdose or infections, as well as the general improvement of the individuals' quality of life [15]. The available pharmacological interventions prevent the appearance of withdrawal symptoms and reduce craving, also increasing adherence to the psychotherapy. First, we will address the three different approved drugs on the market [19]. Although the rate of success, measured by maintenance of abstinence, has been greatly improved with the existing treatments, there is still room for further improvement. In a second part of this chapter, we will also refer to new treatments under development, both in preclinical models and in clinical trials. These new drugs are focused on different neurotransmission systems, which are altered by the neuroadaptive changes induced during the addictive process.

2. Current approved pharmacological treatments for opioid addiction

2.1 Opioid agonist therapies

The great percentage of withdrawn patients who relapse into drug use [20] makes opioid maintenance therapy the first-line treatment in most cases. Ideal agents for substitution maintenance therapy are those with a high affinity for μ-type opioid receptors showing long-term action. Methadone and buprenorphine, as potent and long-acting opioid agonists, are usually prescribed for opioid substitution therapy, and both constitute the most effective treatments for opioid dependence [22].

2.1.1 Methadone

Methadone is a safe, efficient, and effective treatment for heroin addiction [23]. This μ-opioid receptor agonist was introduced in the USA by Eli Lilly and Company as an opioid analgesic in 1947. Methadone maintenance treatment began at the Rockefeller Hospital (1965) with the aim to develop an effective and long action pharmacotherapy that targeted opioid receptors. In these initial clinical trials, patients received safe doses (20–40 mg) once a day, and over time, the dose was adjusted to avoid withdrawal symptoms and reduce craving [17]. Since 1964, a great number of studies have documented the safety, efficacy, and effectiveness of methadone pharmacotherapy for heroin addiction [23].

The National Institutes of Health (NIH) at the end of the 1990s supported methadone maintenance pharmacotherapy for heroin addiction. Nowadays, half of the problematic opiate users are under maintenance treatment, with more than 60% receiving methadone [24]. Elevated retention rates with a noteworthy decrease of illicit opiate use have been observed under methadone maintenance treatment [21, 25–27]. In addition, there are reductions of other associated problems such as intravenous drug use, crime [28–30], and improvement of social functioning [31]. Later studies reported that prolonged methadone maintenance normalized the immune system function in heroin addicts [32], as well as the altered stress response [33]. Methadone is also well suited with performance of complex cognitive tasks [34]. Regarding its efficacy, according to a recent Cochrane meta-analysis, methadone and buprenorphine appear to be equally effective [35].

Regardless of the positive effects of methadone, one of the main difficulties of methadone maintenance treatment is the stigma accompanying the methadone clinics. In order to solve this, maintenance programs aim to rehabilitate patients by reassigning addicts from a traditional clinic to a medical office for ongoing treatment. The concept of medical maintenance carefully emulates the treatment of chronic diseases, such as insulin-dependent diabetes [32].

On the other hand, there are specific drug interactions of methadone [36], for example, the antituberculosis agent rifampin or the anticonvulsant phenytoin [37–39]. Methadone can also inhibit gonadotropin-releasing hormones, lowering testosterone levels [40, 41]. Finally, another recognized effect of methadone is the QT prolongation [42]. Patients who undergo prolonged QT intervals must switch to a treatment with buprenorphine, which does not affect it [43]. Several countries, including Germany and Austria, have alternative treatments for opioid maintenance, such as Levomethadone (purified methadone) [44], which exerts its pharmacologic effects mainly via agonism of μ-opioid receptor.

2.1.2 Buprenorphine

Buprenorphine and the combination buprenorphine-naloxone were also introduced as a possible treatment for opioid use disorder. This medication is characterized by a better side effect profile, lower abuse potential, and good availability when compared to methadone [3]. Buprenorphine is a μ-receptor partial agonist that can reduce opiate cravings, prevent opiate withdrawal, but at the same time blocks the effects of other more powerful opiates [45]. As partial agonist, buprenorphine presents a safety profile with respect to other μ-opioid-receptor agonists and can be more easily adjusted to the desired effect [46]. Although buprenorphine can be the first-line medication over methadone to treat opioid addiction, as it has considerable less abuse potential, its efficacy is limited when treating severe opioid use disorders. Due to the displacement of a stronger opioid by a weaker

one, buprenorphine can precipitate withdrawal symptoms [33, 47]. To increase the adherence to this treatment, patients should be at least in mild withdrawal [48].

To avoid diversion, buprenorphine is usually combined with the specific opioid antagonist, naloxone. In 2006, it was introduced in the European market as a sublingual combination tablet. Several works have established the efficacy of buprenorphine-naloxone as a maintenance medication [49–51] not only for prescription opioids but also for heroin addiction [52, 53]. Numerous meta-analyses have determined that buprenorphine produces successful results in heroin dependence, with no deficiency with respect to being abstinent of illicit opioid use [54, 55]. However, methadone was found to be superior to buprenorphine in overall treatment retention [56]. Buprenorphine therapy not only improves the overall individuals' quality of life but also decreases overcrowding in emergency departments [57, 58].

From a pharmacological point of view, buprenorphine has important advantages over methadone besides the lower risk of overdose [41, 59]. It is preferable for treatment of opioid dependence in those patients with HIV/AIDS [60, 61] and for pregnant opioid users [62]. On the other hand, when buprenorphine is combined with respiratory depressants, such as alcohol or benzodiazepines, it results in sedation, coma, or even death [63]. Furthermore, patients who do not know about the pharmacology of buprenorphine and use additional opioids seeking a "high" are at risk of an overdose when the effects of buprenorphine wear off [55, 64, 65].

2.2 Opiate antagonist therapies

The antagonist therapy blocks or reduces a biological response by binding to and blocking a receptor rather than activating it like an agonist. Naloxone and naltrexone, the opioid antagonist treatments most accepted and commonly used, prevent and reverse opioid effects by mainly blocking the μ-opioid receptor. Both are employed for quick detoxification if there is an overdose and to prevent relapse [66]. Naloxone is a short-acting non-selective opioid antagonist that reverses an opioid overdose. Overdose is a common event for those who use opioids and is the leading cause of death in this population [67, 68]. It quickly crosses the blood-brain barrier and can reverse morphine-induced respiratory depression within 1–2 min [69].

Different studies support the effectiveness of community-based naloxone training and distribution programs in reducing overdose deaths [24, 70, 71]. Naloxone is considered a safe drug to use with little probability of complications, since it has no agonistic activity at the μ-opioid receptor [23]. Since opioid abuse has been declared an epidemic in the USA [4], naloxone has been made more accessible to the relatives of opioid users, which decreases potentially fatal overdoses around 30–40% [72, 73].

Naltrexone is an opioid receptor antagonist that blocks the euphoric and reinforcing effects of opioids consumption, being mainly used for detoxification programs [74–77]. However, the main disadvantage of the use of this antagonist is the low rate of adherence to this treatment, since less than 20% of patients continue opioid antagonist treatments after several months [78]. Nevertheless, with highly motivated patients or dependent people who cannot be included in the methadone program, naltrexone maintenance therapy can be proposed as a successful approach for treating opioid addiction [79]. Furthermore, it has the advantage of not generating tolerance and/or dependency [80]. In the last years, a new intra-muscular depot formulation of naltrexone has been approved, being useful in reducing the days-of-heroin-use and relapse rate compared with a placebo [81, 82]. This depot naltrexone is taken once monthly, and several studies have shown good outcomes compared to placebo in decreasing craving in naltrexone-treated patients [83].

These extended-release naltrexone formulations address the compliance problems that are often found with oral administration [84]. However, a recent comparative study shows that the extended-release naltrexone presents more difficulties in terms of induction and ongoing care with respect to other buprenorphine products, such as the sublingual film of buprenorphine-naloxone [85].

Nevertheless, to date, the extended-release naltrexone is, together with methadone and buprenorphine, the most recommended pharmacotherapy for opioid use disorders, as it has shown superiority with respect to placebo treatment and counseling [83, 86, 87].

3. New pharmacological therapies in development of opiate addiction

Drug addiction induces significant changes in numerous neurotransmission systems [1], which became new therapeutic targets to treat opioid addiction. Therefore, new pharmacological targets are constantly being developed to improve opiate addiction treatment. This second part of the review will offer an overview of the most promising agents under development and we will also discuss the recent advances in neuroinflammation and the pharmacogenetics field.

3.1 Drugs acting on opioid receptors

With the aim of increasing the efficacy and adherence of treatments, numerous studies are testing new approaches to the currently approved medications. For example, the newest buprenorphine subdermal implant called probuphine [88], which was approved by the FDA in May 2016, is prescribed to those patients who have achieved a sustained clinical stability with low-to-moderate doses of a transmucosal buprenorphine-containing product.This implant guarantees non-fluctuating blood levels of buprenorphine continuously for 6 months improving patient compliance [89].

There is growing interest in the slow-release oral morphine (SROM), as a potential effective candidate for maintenance treatment [90–92]. This medication is given once daily, and it suits those individuals who cannot tolerate methadone, respond poorly to other available treatments, or show a prolonged QT [93–95]. However, the last Cochrane meta-analysis reported that there is not enough evidence to confirm the effectiveness of SROM for opioid maintenance, as only three inconclusive studies exist [96].

Tramadol, a reuptake inhibitor of serotonin and norepinephrine, produces a metabolite that moderately acts as a μ-opioid receptor agonist [97]. Recent clinical trials have demonstrated for tramadol the same level of treatment retention and opioid withdrawal symptom suppression as buprenorphine, suggesting that this is a promising and valuable medication [98, 99]. However, although it has been used in the management of acute withdrawal, its use for maintenance treatment as a harm reduction approach has not been assessed systematically. A recent pilot study of tramadol on long-term maintenance in patients with opioid use disorders showed that most of them were able to achieve and maintain abstinence for at least 6 months [100].

3.2 Dopaminergic compounds

It is well known that dopamine (DA) neurotransmission is a common mechanism of drugs of abuse, although the use of DA compounds has not been successful [22]. Numerous preclinical studies have tested the efficacy of different DA antagonists. Acute administration of the DA D3 receptor antagonist SB277011

reduces the reinforcing effects of different drugs of abuse and diminishes opiate withdrawal syndrome [101]. The well-known antipsychotics, aripiprazole (partial DAD2 and 5HT1A agonist and a 5HT2A antagonist) and risperidone (atypical antipsychotic), block context-dependent induced relapse. Risperidone also inhibits reinstatement into heroin seeking due to environmental cues but fails to block relapse induced by priming doses [102]. In the same line, aripiprazole inhibits the conditioned place preference (CPP) induced by morphine [103]. An ongoing clinical trial is evaluating aripiprazole effects to prevent relapse to cocaine use in patients being treated with methadone, as they could return to cocaine consumption, even when they are involved in a drug treatment program [104].

3.3 Glutamatergic compounds

Preclinical studies show that reinstatement of morphine CPP is mainly mediated through glutamatergic neurotransmission [105]. NMDA receptors modulate nociceptive signals in conjunction with opioid receptors, and after continuous morphine treatment, both receptors suffer a desensitization, which mediate analgesic tolerance [22]. Therefore, NMDA receptor antagonists can prevent the development of morphine tolerance. Ifenprodil, an NMDA antagonist, prevents the development, maintenance, and reinstatement of morphine-induced CPP, as well as reinstatement of heroin-seeking self-administration [106].

Another well-known NMDA antagonist is memantine. Animal and human studies have shown positive results in reducing opiate withdrawal and preventing relapse [107–109]. However, clinical trials have not found significant differences in treatment retention, heroin consumption, or craving with respect to placebo [110]. Although memantine administered in combination with naltrexone can improve the emerging symptoms during the early phase of treatment, this combination did not induce significant improvement in preventing relapse [111].

The nitric oxide synthase (NOS) is a neural retrograde messenger molecule involved in several opioid effects. It has been reported that NOS upregulation takes place during the development of opioid dependence [112] and its inhibition blocks opioid dependence [113, 114]. In addition, administration of NOS inhibitors diminishes the development of morphine-induced CPP [106].

3.4 GABA compounds

Baclofen is a GABA-B receptor agonist approved for spasticity treatment, and early preclinical studies suggested that it could promote abstinence from a variety of drugs of abuse [115], such as cocaine, ethanol, nicotine, and methamphetamine [116–119]. Baclofen also reduces morphine withdrawal signs in morphine-dependent animals [120, 121] and disrupts reconsolidation of conditioned reward, facilitating the extinction of the morphine-induced CPP [122]. Assadi and coworkers [123] performed a clinical trial to evaluate the possible benefit of baclofen in the maintenance treatment of opioid addicts and found that the baclofen group presented increased treatment retention being superior to placebo in terms of opiate withdrawal syndrome and depressive symptoms.

An effective add-on therapy combined with methadone or buprenorphine is pregabalin and gabapentin, which are approved for treatment of epilepsy, neuropathic pain, or fibromyalgia [124]. These medications do not act directly on GABA receptors or transporters [125] but modulate the α2-delta subunit of calcium channels, preventing the release of neurotransmitters like glutamate [126]. Both medications prevent opioid tolerance and dependence and reduce withdrawal symptoms in humans and preclinical models [127–129].

3.5 Cholinergic compounds

Numerous studies have demonstrated that the cholinergic system is also implicated in opioid addiction, as chronic morphine administration is associated with changes in gene expression in the cholinergic system, and it increases cholinergic neurons in the laterodorsal tegmental nucleus. Administration of nicotinic antagonists reduces withdrawal symptoms in rodents [130], which suggests that nicotine receptors might be a potential pharmacotherapeutic target for opioid detoxification. Furthermore, a relatively recent study evaluated the role of the α4β2 nicotinic receptors as a potential therapeutic target to treat morphine dependence [131]. A recent clinical trial has evaluated the effects of varenicline, a α4β2 partial agonist and α7 full agonist, usually employed for smoking cessation. Varenicline was effective in opioid detoxification patients, as opioid withdrawal scores decrease with respect to those patients receiving a placebo [131].

Cholinesterase inhibitors, currently used to treat Alzheimer's disease, including donepezil, rivastigmine, and galantamine, increase cholinergic activity and can be potential therapeutic targets in opioid abuse and dependence treatments [132]. Preclinical models have demonstrated that these cholinesterase inhibitors prevented morphine tolerance and attenuated the acquisition and expression of morphine CPP [133].

3.6 Cannabinoid compounds

There are many studies suggesting the potential action of the endocannabinoid system in opioid dependence [134, 135]. Cannabidiol is a natural active metabolite of the *Cannabis sativa* plant, which is currently being explored for its potential anti-addiction properties [135]. It is the second most abundant cannabinoid present in the plant [136], and interestingly, it does not bind directly to cannabinoid receptors but acts as an inverse agonist at both types CB1 and CB2 [137]. Regarding this, cannabidiol has been shown to attenuate the cue-induced reinstatement of heroin seeking [138] and reduces the rewarding properties of morphine in rodents [139]. There is currently a clinical trial examining the effects of cannabidiol on drug craving in abstinent heroin-dependent subjects (ClinicalTrial.Gov identifier: NCT02539823). In addition, cannabidiol, when combined with a potent opioid like fentanyl, is well tolerated, confirming that cannabidiol would be safe in the case of a relapse in abstinent heroin abusers [140].

3.7 Neuroinflammation

The neuroimmune response is an important but relatively poorly understood process in the development of drug addiction. Research is now setting up opportunities for the development of new pharmacotherapies targeting neuroimmune dysfunction. Opioids induce direct and indirect adaptations in the peripheral and central immune systems [141] with a clear relationship between opioid dependence and inflammatory processes [142]. Opioids, such as morphine and heroin, act directly on macrophages and lymphocytes, which produce changes in the CNS, resulting in neurotoxicity [143–145]. Preclinical models show that chronic morphine treatment increases proinflammatory cytokine levels and overactivates the glia [146, 147]. The consequences include dendrite atrophy, abnormal neurogenesis, and neurodegeneration [148]. To sum up, opioids act to generate the release of proinflammatory cytokines, which induce the activation of the inflammatory response, and finally, this response induces changes in the architecture and functioning of the brain. Neuroinflammation derived from opioid consumption is implicated in

tolerance and dependence processes based on results obtained in animal models [149–151]. Anti-inflammatory cytokines, such as the IL-10, which are well tolerated and safe in other inflammatory diseases, could be used as pharmacotherapy in addiction [152]. For example, gabapentin upregulates the anti-inflammatory cytokine IL-10 in rats [128], thus reducing inflammation. Ibudilast prevents glial cell activation, inhibiting production of proinflammatory cytokines (IL1β, IL-6, TNF-α), and increases the secretion of anti-inflammatory mediators like IL-10 [153]. Clinical trials are currently evaluating if this medication, or other glial activation inhibitors, can prevent opioid withdrawal symptoms [154].

On the other hand, peroxisome proliferator-activated receptors (PPARs) mediate anti-inflammatory and neuroprotective processes [155]. Specifically, PPARγ is strongly implicated in reward processing and motivation [156], as they are located in VTA DA neurons and modulate DA release [157], which suggests its potential role in addiction. Currently, preclinical studies have tested the PPAR-γ agonist pioglitazone, an anti-inflammatory medication, as a treatment for opioid dependence, attenuating morphine withdrawal syndrome in rats [158].

3.8 Pharmacogenetics and epigenetics

Pharmacogenetics focuses on selecting the most adequate treatment for specific patients, based on their genetic profile and thereby increasing the therapeutic action of the medication. Its goal is the discovery of gene interactions that increase the success rate of treatments [22]. There are variants of gene-encoding proteins implicated in opioid pharmacokinetics and pharmacodynamics that make the patient respond better or worse to a specific treatment. Most studies focus on genes related to the therapeutic response to methadone and buprenorphine [159]. For example, two gene interactions are determinant for the response to methadone. First, there is the ABCB1, the gene encoding the P-glycoprotein efflux transporter, of which methadone is a substrate. People with variants of this gene (subjects with a wild-type and 61A haplotype combination or homozygous for the 61A) show lower methadone requirements. On the other hand, people with the variant 118A/A in μ-opioid receptor 1 gene (MOR1) show higher methadone requirements [160]. Regarding buprenorphine, the frequency of the gene polymorphism (SLC6A3/DAT1) allele 10 in the DA transporter is much higher in non-responder individuals [161]. These studies reveal the relevance of considering genetic variants when considering treatments with methadone or buprenorphine.

Currently, it is known that it is not only the polymorphisms that we inherit but also how they are expressed, what really matters in genetics. Epigenetics studies the reversible modifications to chromatin and their potent effects on gene expression regulation. Biochemical modifications, such as DNA methylation, histone modification, or micro-RNA expression, can change the pattern of the cell's gene expression [162]. Consequently, such epigenetic changes can modify drug efficacy and its adverse effects, being necessary to take them into account in clinical pharmacology [163]. Currently, the role of epigenetics in personalized pharmacotherapy has been under-explored [164]. This field of research has increased scientific interest in the last years, as changes in DNA methylation or histone modifications alter gene expression, which affects reward, craving, and relapse [165]. For example, in opiate addiction, several changes have been reported in the μ-opioid receptor 1 (OPRM1) gene expression due to the hypermethylation of this gene's promoter [166, 167]. Increased DNA methylation can be a predisposing factor for the vulnerability to heroin addiction or it can be a consequence of it. This is a new and exciting unexplored field that could offer promising results in future years.

4. Conclusion and future directions

Opioid addiction is a chronic relapsing brain disease, being a major medical and social problem. In the past 12 years, several countries are suffering a rise in opioid consumption, not only in its recreative use but also in opioid prescriptions and related misuse and abuse [5]. The high rate of relapse observed in opioid addicts forces the use of maintenance therapy with substitution opiates to reduce damage and to avoid the consumption of illegal opioids, such as heroin. Although the currently approved pharmacotherapies for opioid addiction are effective and encourage patients to stay in treatment, there is still much room for improvement [168]. Methadone, buprenorphine, and extended-release naltrexone are currently the most effective treatments to attenuate the illicit intake of opioids and, together with psychosocial therapy, constitute the best combination to succeed in the treatment [18]. The number of new pharmacological targets is constantly increasing, but frequently, initially promising preclinical studies result in failure in the clinical trials. However, we should be optimistic, since great advances have been made in recent years, but much remains to be improved in a disease as important and complex as opiate addiction.

Acknowledgements

This work was supported by Ministerio de Economía y Competitividad (MINECO), Dirección General de Investigación PSI2014-51847-R and PSI2017-83023-R. Instituto de Salud Carlos III, Red de Trastornos Adictivos (RTA) RD12/0028/0005 y RD16/0017/0007 and Unión Europea, Fondos FEDER "una manera de hacer Europa." We wish to thank Guillermo Chulia for his English language editing.

Conflict of interest

None.

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