

# Expert Opinion

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## Naloxone treatment in opioid addiction: the risks and benefits

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Naloxone is a non-selective, short-acting opioid receptor antagonist that has a long clinical history of successful use and is presently considered a safe drug over a wide dose range (up to 10 mg). In opioid-dependent patients, naloxone is used in the treatment of opioid-overdose-induced respiratory depression, in (ultra)rapid detoxification and in combination with buprenorphine for maintenance therapy (to prevent intravenous abuse). Risks related to naloxone use in opioid-dependent patients are: i) the induction of an acute withdrawal syndrome (the occurrence of vomiting and aspiration is potentially life threatening); ii) the effect of naloxone may wear off prematurely when used for treatment of opioid-induced respiratory depression; and iii) in patients treated for severe pain with an opioid, high-dose naloxone and/or rapidly infused naloxone may cause catecholamine release and consequently pulmonary edema and cardiac arrhythmias. These risks warrant the cautious use of naloxone and adequate monitoring of the cardiorespiratory status of the patient after naloxone administration where indicated.

**Keywords:**  $\mu$ -opioid-receptor,  $\mu$ -opioid-receptor antagonist, addiction, naloxone, opioids

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### 1. Introduction

Although opium has been in use for many centuries, opioid addiction only became a major global problem since the mid 1800s [1]. In the US alone, almost 3 million people aged > 12 years have used heroin, of which 326,000 people received treatment for heroin abuse [101]. In Europe, 1.2 – 2.1 million people are known to be problematic drug users, most of whom use opioids (often in combination with other [illicit] drugs) [102,103]. Of these drug abusers, 450,000 people receive treatment for their addiction. Besides the fact that addicts are more likely to develop mental illness or exhibit criminal behavior, they are also at risk for fatal overdose and various infectious diseases, such as hepatitis B and C and HIV. The number of drug-related deaths in EU member states is estimated to be in the range of 7000 – 9000 per year [103]. Opioid addiction can, therefore, be viewed as a major medical and social problem.

The recent advancements in the understanding of the neurobiology underlying addiction-related behavior contributed to the recognition that opioid addiction is a serious complication of chronic opioid intake in some individuals (note that patients receiving opioids for chronic pain do not necessarily develop addiction). Addiction is nowadays considered a chronic disease of the brain rather than a mental illness carrying a social stigma [2]. New perspectives in the neurobiology of opioid addiction offer unique opportunities for the development of novel treatment strategies. However, as the disease has a multifactorial etiology, treatment must always be multidisciplinary, combining both pharmacologic and psychologic interventions. The pharmacologic interventions are either aimed at detoxification and permanent abstinence from illicit drugs, or at the attenuation of (often protracted) withdrawal

symptoms using opioid replacement therapy. Although sometimes complete abstinence is achieved, often lifelong substitution is the chosen therapy mode. Methadone substitution therapy is the main cornerstone in the treatment of opioid addiction, although in some countries a clear shift is seen in treatment approach with buprenorphine rather than methadone being the first-choice substitution therapeutic [3].

This short review discusses some of the pharmacologic strategies of opioid addiction treatment with special focus on the benefits and risks of the non-selective opioid-receptor antagonist, naloxone.

## 2. Addiction and the $\mu$ -opioid receptor

Opioids exert their effects through specific opioid receptors. The existence of three subtypes ( $\mu$ ,  $\kappa$  and  $\delta$ ) is accepted. The  $\mu$ -opioid receptor subtype, especially, mediates the positive reinforcing effects of heroin and other illicit opioids. This receptor subtype is, therefore, considered crucial in the development of opioid addiction [4]. Dedicated *in vivo* studies have shown that mice lacking the  $\mu$ -opioid receptor (exon 2  $\mu$ -opioid receptor gene knockout mice) display less self-administration of morphine and reduced conditioned place preference [5], underlining the importance of the  $\mu$ -opioid receptor in the development of opioid addiction.

Drugs of abuse, in general, overstimulate those neural systems in the brain that are normally reserved for the response to natural reward systems. In this respect, the mesolimbic dopamine system, as well as the nucleus accumbens, is considered a relevant part of the ventral tegmental area in the midbrain [6,7]. Acute administration of drugs of abuse induces high levels of dopamine being released in the nucleus accumbens, resulting in an increased feeling of reward. Opioids cause dopamine release by inhibiting the  $\gamma$ -aminobutyric acid-ergic inhibition of dopamine release in the ventral tegmental area, a typical part of the midbrain with a high density of  $\mu$ -opioid receptors [8]. Overstimulation of dopamine results in stronger deregulations of the natural reward pathways (sensitization and tolerance) and learning processes in the brain (reinforcement) [5].

Abrupt abstinence from opioids or the administration of  $\mu$ -opioid-receptor antagonists in opioid-dependent persons will produce the opioid withdrawal syndrome. Signs and symptoms of this syndrome include negative moods, irritability, muscular and abdominal pains, gastrointestinal complaints (nausea, diarrhea), sweating, lacrimation, malaise and insomnia [9]. Symptoms usually start 6 – 12 h after the last dose of a short-acting opioid and 36 – 48 h after the last dose of a long-acting opioid, such as methadone. The duration of the syndrome is variable. Some studies report a duration of no more than 7 – 14 days, whereas others also describe a more prolonged withdrawal syndrome lasting from several weeks to a few months. Although the syndrome is not life threatening, many patients experience difficulties completing this initial phase of the therapy [10].

## 3. Pharmacologic treatment strategies in opioid addiction

Treatment of opioid addiction should primarily be aimed at reduction of illicit drug use (next to stabilizing the social functioning of the patient and improving his or her quality of life). This can be done by either gaining control of the patient's drug use by drug replacement therapy or by withdrawing the patient from all opioids (detoxification). It is, however, insufficient to regard complete withdrawal as the ultimate therapy; addiction is a chronic disease (reflected in long-term changes in the brain) and should, therefore, be treated as such. Nowadays, most patients receive maintenance therapy consisting of  $\mu$ -opioid receptor agonists or a combination of  $\mu$ -opioid-receptor agonists and antagonists.

Potent and long-acting opioid agonists with low-intrinsic efficacy are considered good candidates for opioid replacement therapy. Examples of such opioids are methadone and buprenorphine. Methadone is a full agonist at the  $\mu$ -opioid receptor, buprenorphine a partial  $\mu$ -opioid-receptor agonist. This characteristic makes buprenorphine an attractive alternative for methadone, because low-efficacy agonists, are associated with a lower abuse potential compared with relatively higher efficacy agonists such as methadone. Furthermore, the partial agonist, buprenorphine, has a better safety profile than full  $\mu$ -opioid-receptor agonists, indicating that it can be more easily titrated to the desired effect even at high doses [11]. In addition, its unique slow receptor association/dissociation characteristic at the  $\mu$ -opioid receptor contributes to the extended duration of action following single-dose administration [12].

Opioid antagonists, such as naloxone and naltrexone, reverse and prevent opioid effects by blocking the  $\mu$ -opioid receptor. As discussed in Section 2,  $\mu$ -opioid-receptor blockade causes the occurrence of acute withdrawal symptoms in opioid-dependent individuals.  $\mu$ -Opioid-receptor antagonists are widely used in rapid and ultra-rapid detoxification to facilitate the transition from dependence to abstinence. Antagonists can also be used to prevent relapse, as  $\mu$ -opioid-receptor occupancy by opioid antagonists results in a decreased effectiveness of administered opioids. This diminishes the reinforcing effects of heroin and potentially the association between opioid use and conditioned stimuli [9].

## 4. Pharmacology of naloxone

For many years, the development of non-addictive opioids, with the beneficial analgesic action of morphine but devoid of any addictive properties, has been considered an important objective. During the twentieth century, various morphine-like substances were synthesized and tested for their non-addictive properties. Nalorphine, a derivative of morphine, was shown to reverse most of morphine's typical effects at relatively low dose (while inducing analgesia at high dose). In addition, nalorphine precipitates the abstinence syndrome in opioid addicts. Although nalorphine showed promising

blocking properties, the dysphoric effect of this opioid discouraged its widespread clinical use [13]. Additional dedicated structure–activity studies led to the discovery of naloxone. Naloxone, an allyl derivative of noroxymorphone, was synthesized first in 1960. The development of naloxone was encouraged by the need for a real opioid antagonist (in contrast to the partial agonist, nalorphine) devoid of any agonistic activity at the various opioid receptors [14]. Naloxone is a non-selective opioid antagonist at the  $\mu$ -,  $\delta$ - and  $\kappa$ -opioid receptors. Naloxone competitively inhibits the pharmacologic effects of opioids and, in line with the classical receptor theory, produces a parallel right shift in the dose-response curves of opioids [15]. When administered to opioid-dependent patients, naloxone induces a severe withdrawal syndrome, as  $\mu$ -opioid-receptor-bound heroin is displaced by naloxone.

Naloxone appears to be readily absorbed after oral administration, but its low bioavailability renders naloxone less suitable for this administration route. Following oral administration, naloxone undergoes extensive hepatic metabolism, indicating high first-pass effect (> 95%). In the liver, naloxone is primarily metabolized into the inactive conjugate naloxone-3-glucuronide. In addition to glucuronidation, naloxone is also metabolized by *N*-dealkylation and 6-oxo group reduction (note that these metabolism pathways represent only minor fraction of total metabolism). Approximately 30% of the unchanged naloxone dose is excreted in the urine within 6 h following intravenous administration; the rest of the dose is recovered as conjugated naloxone metabolites in the urine [16].

In healthy volunteers, the elimination half-life of naloxone in plasma is  $\sim$  30 min. Although the elimination half-time is not expected to differ among opioid-naïve and opioid dependent patients, differences in naloxone distribution in the body may exist. For instance, Handal *et al.* suggest in their review that there may be differences in pharmacokinetics between opiate-dependent and non-dependent persons, reporting a difference in initial plasma concentration of 30% [17].

Naloxone is readily transported across the blood–brain barrier and, therefore, has a fast onset of action in reversing opioid effects [16]. However, the ability of naloxone to reverse opioid effects *in vivo* is mainly determined by the pharmacologic characteristics of the interacting opioid agonist (i.e., the opioid that requires antagonism). For example, the onset of reversal of morphine-induced respiratory depression by naloxone can be established within a time frame of 1 – 2 min. On the other hand, for an opioid with slow  $\mu$ -opioid-receptor association/dissociation kinetics, such as buprenorphine, the interaction with naloxone is rather complex. Not higher doses of naloxone *per se*, but a different mode of naloxone administration (i.e., continuous infusion) is indicated to reverse buprenorphine-induced respiratory depression [11,12].

As naloxone is devoid of agonistic activity at the  $\mu$ -opioid receptor, it is regarded as a safe drug to use. This notion persists despite earlier clinical experiences showing that naloxone use may (under certain specific circumstances) cause serious

and possibly life-threatening side effects, such as pulmonary edema, cardiac arrhythmias, hypertension and cardiac arrest [18–20]. It is important to note that all of the patients described in these reports were postoperative patients experiencing (severe) pain and stress. In a more recent prospective study [21] in comatose patients due to opioid overdose, 453 patients were treated with naloxone. Six patients suffered from severe complications (asystole, pulmonary edema and epileptic seizures), corresponding to 1.3% of the treated population. However, the exact relationship between naloxone treatment and the occurrence of the severe complications was not clear. The possibility that these complications were related to the initial hit (i.e., the opioid overdose) could not be excluded. The primary reason for the development of cardiorespiratory complications after naloxone therapy is the sudden release of central catecholamines [21]. Especially when naloxone is administered shortly after the occurrence of opioid-induced vasodilation (this may occur just minutes after the opioid is administered via the intravenous route and is visible as a sudden drop in blood pressure) or the patient is sympathetically unstable (due to pain or stress), high-dose naloxone and/or rapidly infused naloxone (i.e., not titrated) can cause catecholamine-mediated vasoconstriction. This then may cause cardiac arrhythmias and a fluid shift from the systemic circulation to the pulmonary vascular bed, resulting in pulmonary edema [18]. Proper monitoring of patients receiving naloxone is, therefore, mandatory, especially of the patient that just recently received an opioid dose via the intravenous route or the sympathetically unstable patient. Studies in animals and healthy volunteers confirm the safety of naloxone use in patients [22,23], even at higher doses up to 10 mg [24] or following constant exposure to intermediate-to-high concentrations of naloxone during 1 – 2 h [25]. Taking into account the fact that there are only few reports in the literature on naloxone-related complications (as well as taking into account their own experience), the authors consider naloxone a relatively safe drug with little chance of complications.

As an alternative to naloxone, a second  $\mu$ -opioid-receptor antagonist, naltrexone, was synthesized with more favorable pharmacokinetic properties than naloxone. Although naltrexone has a relatively low bioavailability (up to 60%), it is two- to three-times more potent than naloxone [13]. It undergoes extensive hepatic metabolism, but because its metabolite, 6- $\beta$ -naltrexol, is also highly active, oral administration can be effective. Elimination half-life is  $\sim$  4 h, with a far longer half-life (up to 13 h) reported for the active metabolite. Effectively, a dose of naltrexone 50 mg will block the pharmacologic effects of heroin 25 mg for up to 24 h [26]. It is employed in rapid and ultra-rapid detoxification and in abstinence maintenance therapy [27]. When compared with methadone maintenance therapy, naltrexone is the less favorable option, as the lack of agonistic effects reduces compliance [26]. If retention of patients, however, is high enough (for example with highly motivated patients or with patients that cannot be included in a methadone maintenance program), naltrexone

maintenance therapy is an effective way of treating opioid addiction [28].

## 5. Naloxone in the treatment of opioid addiction

### 5.1 Naloxone use in treatment of opioid overdose

The most common use of naloxone is for the treatment of opioid overdose. Heroin overdose is one of the leading causes of death among opioid-dependent patients [103] and non-fatal overdoses are also highly prevalent among these patients. Overdose often occurs after a drug-free period and is related to a reduction of tolerance and hence a relatively increased opioid potency. Naloxone is effective in the treatment of opioid-overdose and opioid-induced coma in hospital practice. Note, however, that it is vital to take into account the specific opioid that is responsible for causing the overdose. Most opioids used by addicts have relatively long half-lives, whereas naloxone has a half-life of only 30 min. As a consequence, respiratory depression, caused by long-acting opioids (methadone, heroin, morphine), returns after the effect of naloxone has worn off [14,29]. It is, therefore, necessary to adequately dose and monitor the patient [30]. The initial naloxone bolus dose required to reverse opioid overdose should be determined clinically, starting from 0.4 mg given as a slow bolus injection, continuing until the patient improves. If after naloxone 4 – 10 mg, the patient shows no sign of recovery, the cause of the respiratory depression is most likely not opioid related. After initial recovery, patients should be started on a continuous intravenous naloxone infusion and closely monitored for signs of deteriorating clinical status for at least 24 h.

It is important to note that the patient may enter an acute withdrawal syndrome after administration of naloxone, with consequent nausea and vomiting. The airway must, therefore, be guarded at all times. Another symptom of acute withdrawal may be patient violence [31] and adequate preparation for this situation in the form of restraints is needed. All this taken into account, naloxone remains the first drug of choice in suspected opioid overdose in the hospital setting.

Because an overdose often occurs outside the hospital setting (i.e., at home or on the street), naloxone may not be readily available and it is, therefore, difficult to treat the patient timely. Both healthcare professionals and opioid addicts themselves regarded the idea of so-called 'take-home naloxone' a good strategy in the prevention of fatal opioid overdose [32-34]. Several pilot studies investigated this intervention strategy and although the sample sizes in the studies were small, results were promising, with 90 – 100% of naloxone administrations preventing death from heroin overdose [35-37].

In the UK (June 2005), naloxone was added to the list of drugs that 'may be administered by anyone for the purpose of saving life in an emergency' (that is, everyone is allowed to administer naloxone to an individual with a suspected opioid

overdose) [38]. It is important to educate both the patient and his or her caretakers (not necessarily healthcare professionals) in the use of naloxone in case of a suspected overdose. The caretakers should learn how to recognize an overdose, how to perform mouth-to-mouth resuscitation and how to administer naloxone (either subcutaneously, intramuscularly or intravenously) [39]. In addition, they should be made aware of the necessity of always alerting emergency medical services, to provide the monitoring and further treatment needed in case of an overdose. Often, fear of the police and subsequent criminalization will halt the bystanders (usually fellow addicts) in calling an ambulance – one more reason for distributing take-home naloxone among addicts, thus providing necessary first aid to their peers [35]. Providing the family, caretakers and friends of opioid-addicted patients are well instructed in the use of naloxone, take-home naloxone could be a helpful strategy in combating fatal heroin overdose.

### 5.2 Naloxone in detoxification and maintenance

The conventional way of detoxification is treating the patients with tapering doses of opioid agonists (methadone or buprenorphine) and/or with clonidine or lofexidine ( $\alpha_2$ -adrenergic-receptor agonists that can relieve the symptoms of withdrawal). The protracted nature of these techniques however, leads to a high number of initial dropouts (dropout rates in the literature are in the range of 30 – 90% [28,40]). This was one of the major reasons for the development of new withdrawal strategies, which take less time and may be more comfortable to the patient. Rapid or ultrarapid detoxification under anesthesia or heavy sedation is one such therapy. It consists of the intravenous administration of an opioid antagonist (usually naloxone). The effect of the ensuing acute withdrawal syndrome (lasting 4 – 6 h) is either treated (or masked) with general anesthesia or heavy sedation (using benzodiazepines), both combined with clonidine and  $\beta$ -adrenergic-receptor blockers (to prevent tachycardia). After this initial phase, patients are introduced on an oral dosing of naltrexone as maintenance therapy, with additional psychologic counseling as support. The effectiveness of this approach has recently been called into question, as there is little evidence of its superiority above 'ordinary' opioid maintenance treatment and it appears to have a higher risk of adverse events. In recent years, a few randomised clinical trials were conducted investigating rapid detoxification [41,42]. All concluded that rapid opioid detoxification had no proven benefits above buprenorphine/clonidine detoxification. As the risk associated with this therapy (e.g., the risk of anesthesia or sedation) is much larger than in the other treatment groups, and the costs are significantly higher, it is generally agreed that this form of treatment should not be pursued further [43].

Naloxone can also be used to speed up clonidine or lofexidine-assisted opioid detoxification (i.e., rapid detoxification with naloxone/clonidine). These  $\alpha_2$ -adrenergic agonists alleviate withdrawal symptoms in detoxifying patients, and have proven to be as effective as tapering methadone doses in

**Table 1. Uses and side effects of naloxone in opioid-dependent individuals.**

Naloxone use	Side effects
Opioid overdose	Acute withdrawal syndrome
Detoxification	Recurrence of respiratory depression
Maintenance (combined with buprenorphine)	Cardiac arrhythmias Pulmonary edema

the treatment of opiate dependence [44]. The addition of an opioid antagonist, such as naloxone, to this form of detoxification therapy, leads to a more intense, but less prolonged, withdrawal syndrome. The exact implications for long-term treatment in the form of antagonist maintenance are not yet clear.

In the past, naloxone has been used as an oral abstinence maintenance agent, but its low oral bioavailability and (very) short duration of action make it unsuitable for this purpose [45]. However, it can be used as test medication before administering naltrexone to possibly dependent patients. For example, if intravenous naloxone causes no or little withdrawal symptoms in these patients, it is safe to administer the more potent and long-lasting naltrexone in an oral formulation [46]. Furthermore, it may be used as diagnostic tool in discriminating between opioid-dependent and non-dependent patients (e.g., the occasional abusers or a patient behaving like an addict, but ailing from another disorder such as diabetes).

### 5.3 Naloxone in combination with buprenorphine

In 2002, sublingual buprenorphine (Subutex™, Reckitt Benckiser) and the combination of buprenorphine and naloxone (for sublingual use only, Suboxone™, Reckitt Benckiser) was approved by the FDA for use in opioid addiction treatment. Because buprenorphine alone, as a (partial)  $\mu$ -opioid-receptor agonist, is subject to abuse, the combination treatment was intended to minimize the abuse and misuse of the compound [47]. As this form of therapy gains in popularity, the use of buprenorphine combined with naloxone needs further consideration. When Suboxone is administered sublingually some opioid withdrawal symptoms are only seen in those individuals who are heavily dependent on heroin and/or recently took heroin. Most likely, the bioavailability of naloxone after sublingual administration is too low to cause severe and protracted withdrawal symptoms. However, when a sublingual dose of Suboxone is administered intravenously, all addicts will experience an immediate opioid withdrawal syndrome [48]. On the basis of the pharmacologic properties of buprenorphine, partial agonism and high affinity at the  $\mu$ -opioid receptor, one would expect competitive displacement of heroin by buprenorphine rather than by naloxone. Surprisingly, however, there is ample evidence that withdrawal symptoms in this particular population (opioid-dependent patients) are caused by naloxone [48,49].

This may be related to the fact that several structures in the brain, and more specifically the opioid-receptor system, are subject to changes following chronic exposure to opioids [2,6], thereby significantly altering the interaction of buprenorphine with the  $\mu$ -opioid receptor. One possibility is that chronic exposure to opioids changes the behavior of intravenous buprenorphine from a partial agonist to a full agonist at the  $\mu$ -opioid receptor with lesser affinity for the receptor than observed in opioid-naïve volunteers. Further studies are needed to elucidate this matter. Several studies [49-52] concluded that buprenorphine/naloxone was a good alternative for either methadone or buprenorphine maintenance therapy. Not much is known about whether or not the addition of naloxone truly prevents the misuse of the combination. Evidence is only circumstantial, as it is difficult to monitor the amount of misuse [53,54].

## 6. Summary and conclusions

Naloxone competitively inhibits the pharmacologic effects of exogenously administered opioids and, in line with the classical receptor theory, produces a parallel right shift in the dose-response curves of opioids. Naloxone is readily transported across the blood-brain barrier and, therefore, has a fast onset of action in reversing opioid effects. Its duration of action is limited due to its short elimination half-life of 30 min. The ability of naloxone to reverse opioid effects *in vivo* is mainly determined by the pharmacologic characteristics of the interacting opioid agonist (i.e., the opioid that requires antagonism).

The most common use of naloxone is for the treatment of opioid overdose both in a hospital and out-patient setting. The safety of naloxone in the treatment of opioid overdose is well established in patients and healthy volunteers over a wide dose range (0.4 – 10 mg). There is a special role for intravenous naloxone in rapid detoxification, in which naloxone is combined with the  $\alpha_2$ -agonist, clonidine, and  $\beta$ -adrenergic-receptor-blocking agents to treat withdrawal symptoms. The effectiveness of this approach has recently been called into question as there is little evidence of its superiority above 'ordinary' opioid maintenance treatment and it appears to have a higher risk of adverse events. Finally, naloxone is used in combination with buprenorphine maintenance therapy. Addition of naloxone minimizes the abuse and misuse of buprenorphine and the buprenorphine/naloxone combination is considered a good alternative for either methadone or buprenorphine maintenance therapy (Table 1).

Although naloxone is relatively safe to use, there are some apparent risks and disadvantages associated with its use. Naloxone induces an acute withdrawal syndrome in opioid-dependent persons. Due to its short half-life its effect may wear off prematurely when used for treatment of opioid-induced respiratory depression. High-dose or rapidly infused naloxone administered to a patient who is overdosed with an opioid given for the treatment of acute pain may

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