In Review

Evidence-Based Treatment of Opioid-Dependent Patients

Wim van den Brink, MD, PhD[1], Christian Haasen, MD, PhD[2]

Objective: To provide an overview of treatment options for opioid-dependent patients.

Method: We screened all published studies on the treatment of opioid dependence, with a special focus on systematic literature reviews, formal metaanalyses, and recent trials.

Results: Both clinical experience and neurobiological evidence indicate that opioid dependence is a chronic relapsing disorder. Treatment objectives depend on the pursued goals: crisis intervention, abstinence-oriented treatment (detoxification and relapse prevention), or agonist maintenance treatment. The high quality of solid evidence in the literature demonstrates that there are numerous effective interventions available for the treatment of opioid dependence. Crisis intervention, frequently necessary owing to the high overdose rate, can be effectively handled with naloxone. Abstinence-oriented interventions are effective for only a few motivated patients with stable living conditions and adequate social support. Agonist maintenance treatment is considered the first line of treatment for opioid dependence. Numerous studies have shown efficacy for methadone and buprenorphine treatment, while maintenance with other agonists is also becoming available to a greater extent. Maintenance treatment with diamorphine should be made available for the small group of treatment-resistant, severely dependent addicts. Other harm-reduction measures can serve to engage individuals with opioid addiction who are not in treatment.

Conclusion: Opioid dependence is a chronic relapsing disease that is difficult to cure, but effective treatments are available to stabilize patients and reduce harm, thereby increasing life expectancy and quality of life.

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Clinical Implications

- Agonist maintenance treatment plus psychosocial support should be widely available and freely accessible for all opioid-dependent individuals.
- New extended release antagonist maintenance treatments are promising but should be reserved for internally motivated and stabilized opioid-dependent patients.
- Prison sentences should be regarded as windows of opportunity for the start or continuation of maintenance treatment and psychosocial rehabilitation.

Limitations

- The literature is based on patients with heroin dependence, whereas in many places, heroin has been replaced as the drug of abuse by illicit prescription opioids.
- New interventions such as heroin-assisted treatment, SROM, and extended release naltrexone have not be studied extensively.
- Many prison-based interventions and harm-reduction measures used with opioid-dependent individuals not seeking treatment have not been tested in RCTs.

Key Words: *opioid dependence, maintenance treatment, detoxification, relapse prevention*

The worldwide annual prevalence of opioid use is estimated to be around 0.4% (1), with great regional differences. Among European countries, the annual prevalence ranges from 0.2% in Greece, Poland, and The Netherlands to 0.8% in Italy and the United Kingdom (2). In the United States, the annual prevalence is about 0.4% (3). In China, it is about 1.2% (4). In Canada, the annual prevalence is about 0.4% (5). In most European countries, heroin is the most prevalent illegally consumed opioid, whereas in the United States and Canada, illegally diverted prescription opioids are increasingly the primary illegal opioids. These include hydromorphone (Dilaudid), oxycodone (Oxycointin), codeine (Codeine), meperidone (Demerol), morphine (MS-Contin), and hydrocodone (Vicondin). In some Canadian locations, heroin is almost absent from the illicit opioid user profiles—for example, Toronto (6) and Edmonton and Quebec City (5).

Opioid dependence is associated with severe physical disorders—mainly HIV and hepatitis C virus infections—that are a consequence of intravenous use, as well as with severe social, psychological, and physical harms that are a consequence of the illegal status of the drug and the chronic nature of the disorder. Opioid dependence is a chronic relapsing disease that is considered to caused by a combination of genetic, drug-induced, and environmental factors (7–9). Treatment of opioid dependence can therefore have the following different aims, depending on the health situation and the treatment career of the individual: crisis intervention directed at immediate survival; cure, represented by abstinence-oriented treatment aimed at stable abstinence and, ultimately, recovery from addiction; or care, represented by maintenance treatment directed toward reducing illicit drug use and drug-related criminality, ultimately resulting in improved health and social functioning.

Abbreviations used in this article

CM	contingency management
IM	intramuscular
LAAM	levo-acethylmethadol
MMT	methadone maintenance treatment
NEPOD	National Evaluation of Pharmacotherapies for Opioid Dependence
RCT	randomized controlled trial
SL	sublingual
SROM	slow-release oral morphine

There are numerous effective pharmacologic and psychosocial interventions available for the treatment of opioid dependence. Despite the different aims of these interventions, they all share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance. The common effects of the different drugs on neural circuits account for the key features of the pharmacologic interventions. Different stages in the addiction process have been identified and are often indicated with terms like initiation, continuation, withdrawal, and relapse. These phases are characterized by predominant actions of specific neurotransmitters, involvement of specific brain structures, and activities in specific neural circuits (see, for example, 10–12). In the first phase, initiation, mu-opioid receptors (endorphins) and dopamine play an important role in the acute reinforcing effects of drug abuse, with the ventral tegmental area and the nucleus accumbens as the primary structures of interest. In the second phase of continued drug use, conditioned responses and drug craving, several neurotransmitters are involved, including dopamine in the nucleus accumbens, corticotrophin-releasing hormone in the amygdale, and glutamate in the frontal-cingulate circuit. In the third phase, detoxification and withdrawal, glutamate and norepinephrine in the locus coerulus seem to be crucial. In the fourth phase, relapse after sustained abstinence, the orbitofrontal cortex, the anterior cingulate gyrus, and the amygdale are important brain regions, with norepinephrine and corticotrophin-releasing hormone representing the brain stress system (stress-induced relapse) and gamma-aminobutyric acid and glutamate representing the compulsive and habit system (cue-induced relapse). The roles of these different processes, the related neurotransmitters, and their interactions are crucial for understanding the therapeutic strategies. For example, one can block the reward process, replace illicit drugs by other less harmful or less addictive compounds, prevent or reduce hyperactivity in the stress axis, or restore the balance between the different neural systems. In the following review of currently available treatments for heroin addiction, we demonstrate that many of these neurotransmitter systems and neural circuits can be succesfully influenced to obtain health benefits.

Crisis Intervention

Heroin overdose is one of the leading causes of death among heroin addicts (13). It is well established that nonfatal overdoses are highly prevalent among those with opioid addiction (14). The short-acting opioid antagonist naloxone is an effective substance for treating respiratory depression and coma in patients with an overdose. One study showed that 23% to 33% of injecting heroin users had taken a nonfatal overdose in the last year and that 43% witnessed a heroin

overdose in another user within the last year (15). Often, heroin overdose occurs in the home and in the company of others.

There is no evidence to suggest that subcutaneous or IM routes of administration are inferior to intravenous administration of naloxone (16). This has prompted a discussion on a new strategy to reduce the risks of overdose by making naloxone available for peer administration in the homes of addicts to prevent fatal overdose (13,17,18). Others have studied the preventive effect of sustained release naltrexone implants, and initial findings support its clinical efficacy in preventing opioid overdose (19).

In a retrospective cohort study, adequately applied bystander cardiopulmonary resuscitation was found to be rare but effective, leading to fewer hospitalizations and a small but important improvement in clinical outcome (20). Such interventions may offer important opportunities to save lives and prevent unnecessary damage. Further, because a recent period of abstinence may lead to reduced tolerance and has been shown to be a time of particular risk, the best way to prevent heroin overdose is to participate in opioid-assisted maintenance treatment. All opioid-dependent individuals opting for abstinence-based treatment need to be made aware of the particular risk of overdose after a period of abstinence. This is especially true when abstinence was temporarily obtained through maintenance treatment with the long-acting opioid antagonist naltrexone. Extended use of naltrexone can result in supersensitivity of the mu-opioid receptors and an increased risk of overdose (21).

Heroin overdose is also one of the leading causes for seeking clinical (mainly emergency department) treatment of heroin addicts, of whom about 1 in 4 enter drug treatment within 30 days after the last overdose (22). This has led to interventions where emergency department personnel are trained to provide drug-treatment information and enhance motivation for treatment.

Treatment of overdose patients should always take into account the specific opioid that caused the overdose, with special emphasis on the half-life of the different opioids. Heroin and prescription opioids such as hydromorphone, morphine, oxycodon, and codeine have a relatively short half-life (2 to 6 hours), and a single dose of naloxone (half-life 1 to 2 hours) is generally sufficient to solve the problem. However, methadone has a much longer half-life (16 to 48 hours), and multiple treatments with naloxone may be necessary to guarantee a stable solution of a potentially life-threatening situation. Finally, the partial opioid agonist buprenorphine has a relatively short half-life (3 to 4 hours), but it has a very strong and long-lasting affinity to the mu-opioid receptors and requires higher dosages of naloxone in the case of an overdose. Taken together, it is crucial to ascertain the type of opioid or the combination of opioids responsible for the overdose and to provide adequate dosages of the antidote along with clinical observation of the patient for at least 24 hours.

Abstinence-Oriented Interventions

Despite the chronic nature of opioid dependence, the primary interest of both professionals and individuals with addictions is still the cure of the disease. A cure is defined as long-term, stable abstinence from all opioids. Abstinence is achieved in 2 phases: a detoxification phase, where opioid use is discontinued, generally by reduction and then termination of the opioid use; and a phase of relapse prevention, in which abstinence has to be maintained. Despite great progress in the treatment of opioid dependence in the last 2 decades, outcomes in abstinence-oriented programs remain poor (23).

Detoxification

During detoxification, various pharmacologic substances can be used to manage withdrawal symptoms, including (partial) opioid agonists, opioid antagonists, and alpha-2 adrenergic agonists. The major goal of pharmacotherapy during detoxification is to relieve the severity of opiate withdrawal symptoms to avoid unnecessary suffering and medical complications (for example, epileptic seizures) and to enhance motivation to continue treatment (24). The various Cochrane reviews on detoxification indicate that the most extensively tested effective strategy for the detoxification of heroin-dependent patients is to replace the illegal short-acting opioid by the long-acting opioid agonist methadone, which is subsequently tapered and ultimately discontinued (25). The process and outcome of long-acting opioid agonist tapering can be improved through additional prescription of a calcium-channel blocker such as nimodipine (26), whereas additional prescription of amantadine does not seem to improve the effectiveness of methadone tapering in heroin-dependent patients with or without a comorbid cocaine dependency (27).

Further, there is evidence that the severity of withdrawal under methadone tapering can be reduced by different psychosocial measures, such as having patients well informed (28), contingency management (29), or counselling (30). A Cochrane review found that psychosocial treatment offered in addition to any pharmacologic detoxification program was effective in terms of completing treatment, results at follow-up, and compliance (31). Kleber suggests combining pharmacologic treatment with behavioural and psychosocial approaches to increase efficacy (32).

Other effective strategies include replacing heroin with the partial opioid agonist buprenorphine, which is subsequently tapered, or abruptly discontinuing heroin, followed by the prescribing an alpha-2 adrenergic agonist (for example

clonidine or lofexidine) to reduce withdrawal symptoms (33,34). The Cochrane review on buprenorphine tapering found it to be more effective than clonidine for the management of opioid withdrawal; no significant differences were found between buprenorphine and methadone in terms of completion of withdrawal, despite quicker resolution of withdrawal symptoms with buprenorphine (33). Buprenorphine's advantages, compared with clonidine, lie not only in its side effect profile but also in its positive effects on well-being and psychosocial variables (35). Buprenorphine can be used for detoxification in an outpatient setting, although the relative efficacy between outpatient and inpatient withdrawal is still uncertain (36). However, Kornor and others suggested that outpatient buprenorphine tapering should be closely monitored, owing to substantial psychological distress and increased risk of death (37). In a recent review, Kosten and O'Connor seem to prefer buprenorphine over methadone as their first-choice opioid tapering and detoxification strategy because withdrawal symptoms with methadone last longer than those with buprenorphine (38). It should be noted, however, that patients on high dosages of heroin are sometimes difficult to stabilize with the partial agonist buprenorphine, which results in withdrawal symptoms and early dropout. A recent proposal is to detoxify individuals with heroin addiction with a single, high dose of buprenorphine (32 mg) because the combination of a high dose, the relative long plasma half-life, and the slow dissociation kinetics of the drug from the opioid receptors seems to create a slow and effective tapering process (39). Finally, extended release injectable buprenorphine has been used to support detoxification with just one IM injection (40,41).

Detoxification can also be supported by alpha-2 adrenergic agonists such as clonidine or lofexidine. Despite more evidence supporting the efficacy of clonidine, it has now been shown that lofexidine is to be preferred because hypotension is less likely to occur with lofexidine (34). This makes lofexidine particularly suitable in a prison context when methadone prescription is not possible (42). Comparing alpha-2 adrenergic agonists with methadone tapering shows some differences—the longer duration of methadone tapering, no difference in completion rates, similar or marginally greater withdrawal severity with alpha-2 adrenergic agonists, earlier resolution of withdrawal under alpha-2 adrenergic agonists, more adverse events for clonidine—but no overall difference in clinical efficacy (34).

In an attempt to shorten the detoxification phase, to increase detoxification completion rates, and to enhance initiation of pharmacologically supported relapse prevention, naltrexone-assisted detoxification procedures with and without heavy sedation or full anesthesia were introduced. According to the Cochrane review, the use of an opioid antagonist (such as naltrexone, naloxone, or both) combined with an alpha-2 adrenergic agonist to ameliorate withdrawal symptoms is a feasible detoxification strategy, particularly as a means of facilitating entry into maintenance with an opioid antagonist (43). The withdrawal syndrome associated with this strategy is likely to be somewhat more severe than in withdrawal management with an alpha-2 adrenergic agonist alone, but signs and symptoms are likely to resolve more quickly, resulting in the overall withdrawal episode being perceived as somewhat less severe than with clonidine or lofexidine alone. However, a high level of monitoring and support is necessary for several hours after initial administration of naltrexone because of possible vomiting, diarrhea, and delirium (43–45). One RCT compared clonidine, clonidine plus naltrexone, and clonidine and naltrexone in combination with buprenorphine (46). After stabilization for as little as 3 days, patients taking buprenorphine reported fewer withdrawal symptoms than did patients in the other 2 groups.

With regard to naltrexone-assisted detoxification under heavy sedation or full anesthesia, the original enthusiasm has changed into skepticism or plain rejection of the whole idea. Despite earlier reports, most patients still experience moderate withdrawal symptoms lasting at least a few days after the anesthetic procedure. In addition, several serious adverse medical events related to the anesthetic procedure were reported. The authors of a report on the first RCT directly comparing naltrexone-assisted detoxification with and without full anesthesia clearly state that heavy sedation or full anesthesia has no place in naltrexone-assisted rapid detoxification (47). Further, in a recent randomized trial comparing naltrexone-induced, anesthesia-assisted detoxification with buprenorphine- or clonidine-assisted detoxification, Collins and others found no difference in withdrawal severity and rates of completion but 3 potentially life-threatening adverse events associated with anesthesia (48). They concluded that the data do not support the use of anesthesia for detoxification. Similarly, a review of the literature found anesthesia-assisted detoxification to be dangerous, owing to the sympathetic outflow if the procedure is not performed properly (49). Two recent Cochrane reviews clearly state that naltrexone withdrawal under heavy sedation or full anesthesia should not be pursued because it does not confer additional benefits in terms of less severe withdrawal or increased rates of commencement on naltrexone maintenance, whereas at the same time, it does lead to an increase in potentially life-threatening adverse events (44,50).

There have been several attempts to develop other pharmacologic opioid-etoxification approaches. One such approach is to use tramadol, a centrally acting analgesic with opioid activity but low abuse potential; preliminary results show clinical efficacy equal to buprenorphine in the detoxification of opioid

dependence (51). Another approach is to use buspirone in the treatment of acute opioid withdrawal, the assumption being that a decrease in serotonergic neurotransmission may be involved in opioid withdrawal symptoms. Initial results found buspirone to be as effective as methadone tapering in alleviating withdrawal symptoms (52). However, more studies are necessary before firm conclusions can be drawn regarding the efficacy of these new detoxification strategies.

Although methadone or buprenorphine maintenance is the preferred treatment for pregnant women with heroine dependency (53–55), naltrexone-assisted detoxification may be an option for women who are unable to stabilize on methadone or buprenorphine and continue to use street drugs. In a series of 18 cases with detoxifications in all 3 trimesters, no neonatal, maternal, or obstetric complications were observed following naltrexone detoxification (56).

Relapse Prevention

Traditional relapse-prevention programs were limited to long-term inpatient treatments that were intended to last at least 9 months and that often used the therapeutic community format. In many countries, this model has been replaced by shorter inpatient treatments generally lasting less than 6 weeks. The positive effects of both long-term and short-term programs are, however, rather limited. In a 3-month follow-up of 242 opioid-dependent patients in residential treatment in the National Treatment Outcome Research Study, 34% of the patients relapsed to heroin use within 3 days, 45% within 7 days, 50% within 14 days, and 60% within 90 days. According to the authors, the results of this study highlight the need to provide aftercare services to help patients maintain the gains achieved during treatment and to avoid the high risk of relapse at this time (57).

One possibility to reduce the risk of relapse to illegal opioid use is long-term prescription of an opioid antagonist such as naltrexone, the "model anti-craving medication" (58). The first obstacle involved in this strategy is the high dropout rate during detoxification, which results in highly selective patient samples in most of the naltrexone maintenance studies (59). In a metaanalytical review, retention was found to be the most important predictor for the effect of naltrexone in treating opioid dependence, and the authors therefore proposed to add counselling (60) or contingency management (61) to naltrexone maintenance treatment. Another important option to improve retention is the use of a sustained release depot formulation of naltrexone. A recent study of this formulation for the treatment of opioid dependence found 60% to 68% retention after 2 months (62). However, the study sample was small, and no direct comparison with oral naltrexone was provided. Therefore, the potential advantages should regarded as promising but not proven.

Once patients are receiving naltrexone maintenance treatment, the results are still not very promising. According to the Cochrane reviewers, a systematic review of the available evidence showed no benefit in terms of retention in treatment, side effects, or relapse results, even compared with placebo (63). This conclusion is corroborated by the findings of the NEPOD study in Australia, which showed that only 4% of the patients in naltrexone maintenance treatment were still in treatment after 6 months (64). Further, relapse prevention treatment with buprenorphine or methadone was preferred by patients over naltrexone (65). Naltrexone maintenance or relapse-prevention treatment should, therefore, be reserved only for those patients who are highly motivated for long-term total abstinence and who are otherwise in a stable and productive life situation, for example, opioid-dependent business executives and physicians (66,67).

Naltrexone-assisted treatment might also be indicated for pregnant women who do not stabilize on methadone or buprenorphine. Naltrexone detoxification and relapse-prevention treatment during pregnancy and thereafter might be a viable option with minimal risks for both the mother and the newborn (56). In a recent case study of a noncompliant pregnant woman, oral naltrexone maintenance was successfully replaced by a 1.8-g subcutaneous implant of naltrexone in poly-DL-lactide acid at 23 weeks' gestation (68). Similar positive reports are available with nonpregnant patients (69,70). In contrast to these positive findings, however, some authors have reported several serious complications with these implants (71). Recently, positive results were reported for the safety and potential effectiveness of a long-lasting IM depot formulation of naltrexone with adequate antagonizing effects up to 5 weeks following the injection (62,72), as well as for subcutaneously implanted pellets with slow-release naltrexone (73).

Another strategy to improve treatment compliance is to combine naltrexone maintenance with voucher-based CM. This strategy involves the provision of vouchers redeemable for goods and services contingent on naltrexone intake and drug-free urine samples. Three studies have demonstrated improved compliance and effectiveness when naltrexone was used in combination with CM (74–76). The additional effect of CM was independent of other support measures (75) and not related to the magnitude of the vouchers (74). In a metaanalytical review, CM was found to increase retention in naltrexone treatment (61). In another review, O'Brien suggests that medications for relapse prevention are most effective in the context of counselling, cognitive therapeutic, and behavioural techniques (58).

In another attempt to improve the outcome of naltrexone maintenance treatment, a nonrandomized (77) and a randomized (78) open-label study suggested that combining

naltrexone with a selective serotonine reuptake inhibitor is more effective than using naltrexone alone. However, the first randomized, placebo-controlled trial in a population of opiate-dependent patients without depression did not demonstrate any lasting effect of the combined treatment (79).

Two other issues related to the prescription of naltrexone deserve special attention: the potential induction of depression by naltrexone and the overdose risk following discontinuation of naltrexone treatment. In a systematic review of the available literature, it was concluded from the equivocal evidence that it is reasonable to assume that there is no demonstrable association between naltrexone and depression or anhedonia and that reduced tolerance to opiates following naltrexone treatment may indeed increase the risk of heroin overdose (60). Therefore, a clear warning to patients is warranted.

Maintenance Treatment

Given the chronic relapsing nature of the disease and the generally disappointing long-term results of detoxification in combination with relapse prevention, stabilization of illegal drug use, improvement of well-being, and reduction of drug-related harm has become the most important treatment modality in many countries. Opioid-assisted maintenance programs are among the most important strategies in this respect because they are associated with reduced heroin use and reduced HIV risk behaviour (80). Considering the high rate of relapse after detoxification, maintenance therapy is currently considered to be the first-line treatment for such patients (81). Opioid-assisted maintenance programs have been implemented in most countries, yet the substance of choice differs from one country to the next. Methadone is the most extensively studied and most widely used substance in maintenance treatment. Other substances include other mu-opiate agonists such as LAAM, codeine, slow-release morphine, and diamorphine, as well as the partial mu-opioid agonist buprenorphine.

According to the most recent Cochrane reviews, methadone, LAAM, and buprenorphine are all proven effective for maintenance treatment, provided that adequate dosages are prescribed (82–84). Another Cochrane review found methadone dosages ranging from 60 to 100 mg daily to be more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment (85). A comparative metaanalysis covering studies between 1966 and 1999 indicated that high dosages of methadone (≥ 50 mg daily) were more effective than low dosages (< 50 mg daily) in reducing illicit opiate use; that high dosages of methadone were more effective than low dosages of buprenorphine (< 8 mg daily); and that high dosages of methadone were equally effective, compared with high dosages of buprenorphine (≥ 8 mg daily), in terms of retention and reduction of illicit opiate use (86). The same metaanalysis found that LAAM was at least as effective as high-dose methadone but that patients treated with LAAM were more likely to leave treatment prematurely (86). Similar conclusions were drawn from an RCT with 4 study arms: low-dose methadone, high-dose methadone, high-dose buprenorphine, and LAAM (87).

Maintenance treatment with LAAM has emerged as very promising, if not better than maintenance treatment with other opioid agonists. In a randomized, cross-over clinical trial with 62 stable methadone patients, most (69%) preferred LAAM over methadone. The main reasons given for choosing LAAM were fewer withdrawal symptoms, fewer side effects, less craving for heroin, and fewer "pick-up" days (88). LAAM maintenance treatment was also shown to be feasible and potentially effective in heroin-dependent detainees in a Baltimore prison: 61% of the prisoners who were initiated on LAAM during imprisonment entered maintenance treatment after release (89), a success rate similar to the findings of a methadone prison program in New York (90). However, in March 2001, the Committee of Proprietary Medicinal Products recommended to the European Commission that marketing authorization for LAAM be suspended, after an association was noted with 7 cases of torsade de pointes, a potentially fatal ventricular arrhythmia (91). For the same reason, the US Food and Drug Administration changed the labelling for LAAM to emphasize that the drug should be used only to treat opioid-dependent patients who fail to show an acceptable response to other adequate addiction treatments (92).

The best studied and most effective opioid agonist for maintenance treatment is methadone (32,93). Treatment outcome in methadone maintenance can be improved substantially with increased dosages (76,94–97) and the provision of adequate psychosocial support (31,76,98). However, as an interim solution prior to entry into a comprehensive MMT program, even MMT without adequate psychosocial care has been shown to increase the likelihood of entry into comprehensive treatment, reduced heroin use, and reduced criminal behaviour (99).

Retention in MMT crucially depends on adequate daily dosages (100). In the US, low dosages of methadone have to a large extent been replaced by higher dosages, as indicated by the observation that in 1988 almost 80% of patients received dosages less than 60 mg daily, whereas this was the case in only 36% in 2000 (101). Recent studies further indicate that methadone dosages between 30 and 60 mg may be effective in suppressing withdrawal symptoms but that dosages of 120 mg or more are needed to eliminate heroin use while in MMT (96,102). It should be noted that very high dosages have been associated with the occurrence of torsade de pointes, similar to the situation observed in treatment with

LAAM (103); however, cases of torsade de pointes have also been reported for patients receiving a recommended dosage between 60 and 100 mg daily (104). Although adequate psychosocial interventions are likely to increase the effectiveness of MMT, excessive supplementary services such as daycare programs show little added benefit and are not cost-effective (105,106).

Methadone is the first-choice maintenance treatment in most countries, but buprenorphine might be an alternative for heroin-dependent patients who do not seem to benefit from methadone in adequate dosages (although no empirical data are available for this second-line indication). Several studies have shown efficacy of buprenorphine in maintenance treatment of opioid dependence (for a review of trials, see Ling and Wesson, 66). Further evidence suggests that, compared with MMT, mortality is even lower among patients in buprenorphine maintenance treatment (107).

In addition, buprenorhine could be a safe and feasible alternative for office-based opioid-assisted treatments in primary care. In 2 small-scale US studies, buprenorphine prescription in primary care was associated with good retention (70% to 80%) and reasonable rates of opiate-free urine samples (43% to 64% achieved 3 or more consecutive weeks of opiate-free urine) (108,109). These positive effects were confirmed in a larger trial showing reduced opiate use and craving for opiates under buprenorphine (110). Similar results were obtained some years ago in France (111). For the United States, a consensus statement has been developed on office-based treatment of opioid dependence, using buprenorphine (112).

However, buprenorphine is generally administered as an SL tablet, and therefore it must be water-soluble. As a consequence, buprenorphine tablets can be dissolved and injected, and abuse has already been reported from several countries, especially from countries with office-based prescription (113). Because of this abuse potential, interest has shifted to the development of a tablet that contains both buprenorphine (good SL bioavailability) and naloxone (poor SL bioavailability). Thus a buprenorphine–naloxone tablet taken by the therapeutic route (that is, SL) should produce a buprenorphine effect, whereas a tablet dissolved and injected intravenously by an opioid-dependent individual produces an opioid-withdrawal syndrome. These assumptions were confirmed in various experimental studies indicating that a 4:1 buprenorphine–naloxone combination has indeed a low abuse potential (114) but equal efficacy with regard to reducing the use of and craving for opiates (110). It should be noted, however, that the additional value of the combination strategy has not been proven in a routine clinical setting.

Finally, a US cost-effectiveness study that used a dynamic model to capture the effects of adding buprenorphine maintenance treatment to an existing treatment system already including MMT showed that buprenorphine maintenance is cost-effective under all scenarios considered, if the price is less than $5 per daily dosage. At $15 per daily dosage, it is only cost-effective if its adoption does not lead to a net decline in methadone use (115). At the same time it should be noted that, in Australia, methadone has been shown to be slightly more effective, cheaper, and thus more cost-effective than buprenorphine as a first-line treatment (116).

An important issue in agonist maintenance treatment is the prescription of methadone to prison-based populations. Several studies in Europe, Australia, Puerto Rico, and Canada have now shown that MMT in prison leads to reduced drug use, drug injection, and needle sharing; that it produces improvements in institutional behaviour; and that it has a positive effect on release outcomes (117–120).

A rather new development is the medical prescription of heroin to chronic, treatment-refractory, heroin-dependent patients—an intervention that has been and will be tested in several countries in Europe and North America (121). In 2 recent reports about the Swiss experience, it was concluded that supervised medical prescription of heroin was associated with good retention (70% over 12 months) and resulted in reduced illicit drug use (both opiates and cocaine), reduced criminality, and improved health outcomes and social functioning (122,123). However, because of design restrictions, no final conclusion could be drawn with respect to the causal role of heroin in the observed benefits (124–126). In a recent report on 2 RCTs that were conducted in The Netherlands, the effect of treatment combining methadone with injectable or inhalable heroin was compared with the effect of treatment using methadone alone; the psychosocial treatment offer was kept constant between the treatment conditions (127). The results of these trials were similar to those of the Swiss trials, but for the first time, the observed improvements could be attributed to the medical prescription of heroin (128–130). Moreover, from a societal perspective, the coprescription of heroin in this specific population was found to be cost-effective, compared with treatment with methadone alone (131). Recently, similar results were reported from a small controlled trial from Spain and from a large RCT from Germany (both unpublished). In a recent Cochrane review, the authors state that, from the currently available results (not including the Spanish and the German data), no definitive conclusions about the overall effectiveness of heroin prescription are possible, owing to the noncomparability of the experimental studies (132). In 2005, an RCT comparing the effectiveness of heroin-assisted treatment and MMT started in Vancouver and Montreal (133). The results of this trial are expected in 2007.

Maintenance treatment has also been described as effective with 2 other opiate agonists: codeine and SROM. Codeine maintenance treatment is only authorized in Germany, where effectiveness comparable to MMT has been described (134). However, owing to its shorter bioavailability, codeine maintenance treatment will probably not have a future place in the treatment of opioid dependence. In contrast, SROM is a promising compound that is complementary to existing substances for maintenance treatment and has been authorized for maintenance treatment of opioid dependence in a few European countries. Several smaller and mostly open-label studies have shown positive results for SROM with respect to retention, reduced heroin use, and (or) improved quality of life (135–139). Further studies will have to confirm these results before the added value of this substance for the treatment of heroin dependence can be established.

Other Harm-Reduction Measures

Maintenance treatment is considered the most important harm-reduction measure. Nonetheless, other harm-reduction measures have been shown to be effective in reducing drug-related health risks. The 2 main measures are the introduction of needle exchange programs and the provision of various forms of user rooms. Needle exchange programs were initiated to prevent the spread of blood-borne pathogens through the exchange and free distribution of syringes and other injection utilities. The effectiveness of needle exchange programs has not only been shown in the reduction of drug-related health problems but also in the reduction of injection frequency and increased entry and retention in drug treatment (140,141). Therefore needle exchange programs can be considered one of the many strategies among the diversified treatment options needed to tackle heroin dependence. This seems also to be true for prison situations, where both MMT and needle exchange programs, separately and in combination, can result in reduced risk behaviour and reduced transmission of blood-borne infections (117,142).

User rooms, which allow drug users to use preobtained drugs in a hygienic, stress-free atmosphere, in some cases with additional health care offers, have been implemented in several countries in Europe (specifically, in Switzerland, The Netherlands, Germany, and Spain), as well as in Australia and Canada. The aims of user rooms are to promote health and reduce risk behaviours and public nuisance. The promotion of health focuses on reducing emergencies associated with the use of heroin—mainly (fatal) overdoses—and on hygienic measures related to the intravenous application of heroin. Several descriptive studies have shown that supervised user rooms can operate safely and have also found significant effects on harm reduction and reduction of public nuisance (143–149). Nonetheless, legal concerns have limited the availability of user rooms and needle exchange programs to regions where federal and state restrictions have been eased and public advocacy for their support has been strong. However, these limited experiences have shown that, when drug abuse issues are treated primarily as medical and public health issues rather than as criminal justice issues, drug-related health problems and public nuisance are reduced, which is in the interest of both those dependent on opioid substances and society as a whole.

Conclusions

Treatment of opioid dependence needs to consider the fact that opioid dependence is a chronic relapsing disorder needing long-term treatment with great emphasis on motivation, psychoeducation, continuity of care, integration of pharmacotherapy and psychosocial support, and finally, a better liaison between the treatment and the judicial system. Therefore, the pharmacologic treatment of opioid dependence needs to be embedded in a comprehensive health care context, and the disorder should not be viewed as a brain disease only. Nonetheless, the notion that opioid addiction is a brain disease that can be effectively treated needs to be promoted to fight existing stereotypes and stigmatization. One way to do so is to promote office-based treatment of opioid-dependent patients, a treatment offer that is most likely to work only when specialized addiction-treatment services are willing to temporarily take responsibility for these patients in times of decompensation or crisis (112).

There are several effective strategies for treating opioid dependence (32,93). According to the extensive body of scientific evidence and broad experience with its use in clinical practice, MMT should now be considered the single most important first-line treatment for opioid dependence (81). Important complementary treatments for patients who do not fully respond to adequate dosages of methadone include the use of other agonist maintenance treatments, the main other substance being buprenorphine (83). For those patients resistant to these treatments, treatment with diamorphine should be considered (132). Harm-reduction measures, such as needle exchange programs or even user rooms, are often necessary to engage individuals with opioid addictions into maintenance treatments or to serve patients who are not yet motivated to enter institutionalized treatment (140).

Detoxification should not be considered a treatment in and by itself and should only be promoted in the context of a well-planned relapse-prevention program. It should be restricted to patients who are still physically fit, psychologically stable, and socially integrated or who have reached that situation after successful treatment in an agonist maintenance treatment program (67,93). The high risk of relapse after detoxification would otherwise be the accepted consequence,

along with the high risk of (fatal) overdose associated with relapse after detoxification (14).

Opioid-dependent patients frequently suffer from physical ailments and other psychiatric disorders. Research has shown that positive results can be obtained when targeted interventions are directed to these additional diseases. Integrated treatments by multidisciplinary teams are a precondition for comprehensive success in treating patients with multiple and complex pathology.

Polydrug abuse is the rule rather than the exception and, therefore, other types of drug and alcohol abuse should always be taken into account. It should be noted, for example, that reductions in illicit opioid use in agonist maintenance treatments often cooccur with reductions in cocaine use but sometimes also with increased alcohol abuse. These patterns should be carefully monitored and treated, if indicated.

Imprisonment is still a common event in the life of an individual with opioid addiction but should never automatically result in discontinuation of an existing treatment (118). On the contrary, imprisonment constitutes a window of opportunity to initiate or restart treatment, with a necessary continuation after release.

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[1]Professor of Psychiatry and Addiction, Academic Medical Center, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands; Director, Amsterdam Institute for Addiction Research, Amsterdam, The Netherlands.
[2]Associate Professor of Psychiatry, University Medical Center Eppendorf, Department of Psychiatry, Hamburg, Germany; Manager, Center for Interdisciplinary Addiction Research, Hamburg, Germany.
Address for correspondence: Dr W van den Brink, Academic Medical Center, University of Amsterdam, Department of Psychiatry, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands; w.vandenbrink@amc.uva.nl

Résumé : Le traitement fondé sur des données probantes de patients dépendants des opioïdes

Objectif : Fournir un aperçu des options de traitement pour les patients dépendants des opioïdes.

Méthode : Nous avons examiné toutes les études publiées sur le traitement de la dépendance aux opioïdes, en mettant l'accent sur les études systématiques de la documentation, les méta-analyses officielles, et les essais récents.

Résultats : Tant l'expérience clinique que les données probantes neurobiologiques indiquent que la dépendance aux opioïdes est un trouble chronique récurrent. Les objectifs du traitement dépendent des buts recherchés : intervention d'urgence, traitement axé sur l'abstinence (désintoxication et prévention des rechutes) ou traitement d'entretien antagoniste. La grande qualité des données probantes confirmées de la documentation démontre qu'il y a de nombreuses interventions efficaces disponibles pour le traitement de la dépendance aux opioïdes. L'intervention d'urgence, souvent nécessaire en raison du taux élevé de surdoses, peut s'effectuer efficacement avec la naloxone. Les interventions axées sur l'abstinence ne fonctionnent que pour quelques patients motivés qui ont des conditions de vie stables et un soutien social adéquat. Le traitement d'entretien antagoniste est considéré être le traitement de première ligne pour la dépendance aux opioïdes. Nombre d'études ont montré l'efficacité du traitement à la méthadone et à la buprénorphine, tandis que l'entretien avec d'autres antagonistes est offert dans une plus large mesure. Le traitement d'entretien à la diamorphine devrait être offert au groupe restreint de toxicomanes gravement dépendants et réfractaires au traitement. D'autres mesures de réduction des méfaits peuvent servir à attirer des personnes dépendantes des opioïdes qui ne sont pas en traitement.

Conclusion : La dépendance aux opioïdes est une maladie chronique récurrente difficile à soigner, mais des traitements efficaces sont disponibles pour stabiliser les patients et réduire les méfaits, augmentant ainsi l'espérance et la qualité de vie.