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Injectable and implantable sustained release naltrexone in the treatment of opioid addiction

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Sustained release technologies for administering the opioid antagonist naltrexone (SRX) have the potential to assist opioid-addicted patients in their efforts to maintain abstinence from heroin and other opioid agonists. Recently, reliable SRX formulations in intramuscular or implantable polymers that release naltrexone for 1–7 months have become available for clinical use and research. This qualitative review of the literature provides an overview of the technologies currently available for SRX and their effectiveness in reducing opioid use and other relevant outcomes. The majority of studies indicate that SRX is effective in reducing heroin use, and the most frequently studied SRX formulations have acceptable adverse events profiles. Registry data indicate a protective effect of SRX on mortality and morbidity. In some studies, SRX also seems to affect other outcomes, such as concomitant substance use, vocational training attendance, needle use, and risk behaviour for blood-borne diseases such as hepatitis or human immunodeficiency virus. There is a general need for more controlled studies, in particular to compare SRX with agonist maintenance treatment, to study combinations of SRX with behavioural interventions, and to study at-risk groups such as prison inmates or opioid-addicted pregnant patients. The literature suggests that sustained release naltrexone is a feasible, safe and effective option for assisting abstinence efforts in opioid addiction.

Introduction

Heroin is used by an estimated 0.4% of the world's population, but heroin-related problems account for nearly 60% of the treatment demand in Europe and Asia [1]. The best candidate explanation for this lies in the comprehensive nature of heroin addiction; the sedative effects of the opioid agonist heroin greatly increase the risk of fatal or near-fatal overdose, while a high incidence of injecting use greatly increases the risk of introducing bacterial, viral or fungal agents due to nonsterile injecting practices. Regular heroin users also have an increased occurrence of mental health disorders, and often engage in the regular use of at least two other illicit drugs [2]. In the USA, diversion and misuse of prescription opioids is an increasing problem [3]. There are environmental factors associated with illicit opioid use, such as engagement in criminal activities, poor living standards and 'less stable environments' (i.e. exposure to violence, accidents, injury and suicide) [4]. All these factors contribute to increase the risk of death from regular illicit opioids to a rate of about 8.6 deaths per 1000 person-years [5]. This risk is heightened following detoxification and discharge from a controlled environment, because opioid receptors are thought to readjust to function without exogenous opioid intake. For example, one study found that the risk of overdose death was 12 times that of the pre-admission risk following discharge from inpatient treatment such as detoxification [6]. Another study found that the risk of mortality was up to 34 times elevated during the first 2 weeks following release from a prison setting [7]. Recovery from heroin addiction often takes several years, with at least occasional relapse and setbacks; it is thus often understood as a chronically relapsing disease [8]. While most of our present knowledge on opioid addiction comes from experience with illicit heroin users, all types of opioid agonists share the same basic neurophysiological pathways and thus the risk of dependence, tolerance, withdrawal, intoxication and abuse.

Present treatment alternatives

Until recently, treatment options for heroin addiction were limited to the following three main alternatives: detoxification followed by long-term residential treatment; opioid maintenance treatment (OMT); and oral naltrexone.

Detoxification followed by long-term residential treatment has been found to result in some reduction in drug use for a large minority of patients, but suffers from problems with retention in treatment and risk of overdose upon discharge [9]. Opioid maintenance treatment maintains or substitutes dependence on heroin via the supervised administration of opioid agonist medications including methadone, buprenorphine or medically dispensed heroin [10]. While OMT is effective in reducing mortality, morbidity and drug-related criminal activity, chief concerns are dropout during the initial months of treatment and that only a minority of patients are able to achieve normal vocational and social functioning. For those who do achieve such integration, there is currently no validated alternative to life-long dependence on the opioid agonists administered daily in OMT.

Naltrexone – an opioid antagonist

Naltrexone induces a competitive antagonism at all the main types of opioid receptors, with some preference for the μ receptor. Although both naltrexone and naloxone were developed based on modifications of oximorphan, the overall affinity of naltrexone for opioid receptors is higher and its half-life significantly longer than that of naloxone. Thus, naloxone is better suited for acute purposes, such as reversing the effects of opioid-induced sedation, while naltrexone is better for scenarios that require prolonged antagonism, e.g. assisting abstinence from opioid agonists following detoxification and/or reducing addiction-related craving. While a full review of these latter types of effects is beyond the scope of this article, the high prevalence of comorbid substance use problems makes them relevant to the overall therapeutic effect, especially for heroin users.

Naltrexone has long been known to cause a reduction in craving sensation for many types of addictive substances, including alcohol [11] and amphetamine [12]. There have also been reports of a similar effect on certain types of compulsive behaviours, such as bodily self-harm [13] and gambling addiction [14]. The precise mechanism for craving reduction has not been determined, but the most likely is that naltrexone causes antagonism of opioid pathways to the nucleus accumbens, reducing the total amount of dopamine released. Naltrexone at very low doses (0.25 mg day^{-1}) seems to reduce the severity and/or longevity of opioid withdrawal during detoxification [15], possibly assisting a restoration of normal opioid receptor functioning [16] and attenuating noradrenergic withdrawal systems [17]. In addition, opioid antagonists like naltrexone affect other biological systems, such as G-protein second messenger systems [18], the immune system [19] and the hypothalamic–pituitary–adrenal axis [20].

Compliance problems with oral naltrexone

Studies of oral naltrexone tablets taken daily or bidaily have generally failed to show superiority over placebo, mostly due to rapid dropout in the active naltrexone group. However, modestly improved results can be achieved when oral naltrexone is taken as part of a compliance-reinforcing scheme, such as contingency management [21]. The lack of clinical success with oral naltrexone was recognized in the first clinical studies of oral naltrexone [22, 23]. Consequently, research efforts were started in order to develop sustained release technologies that would decrease compliance problems by reducing the number of dropout opportunities. As part of development efforts for a sustained release formulation, the following two central characteristics for sustained release naltrexone (SRX) were formulated: (i) for blocking street heroin doses, the minimal plasma level of naltrexone was estimated to be about 1 ng ml^{-1}, although some of this blockade is also provided by the metabolite 6β-naltrexol [24]; and (ii) a clinically useful SRX formulation was thus considered to release naltrexone at levels of 1 ng (ml plasma)$^{-1}$ or above for the duration of at least 4 weeks, with an acceptable rate of tissue-related adverse events. Following more than 30 years of development efforts, this goal has recently been achieved.

Sustained release naltrexone (SRX) formulations

Currently, two main types of sustained release technologies are used to release naltrexone: injectable intramuscular suspension and surgically implantable pellets. This section provides a summary of the data from the literature on the currently available SRX technologies, and their ability to block opioid agonists, such as heroin or morphine. While there are other sustained release technologies available, e.g. for buprenorphine [25], these have not been developed for naltrexone.

Polylactide suspension

The naltrexone release of this class of SRX medications is based on the slow biodegrading of a 380 mg polylactide and naltrexone suspension, providing therapeutic blood levels of naltrexone over a period of 28 days. An intramuscular SRX suspension of this type was recently approved by the US Food and Drug Administration for prescription for

opioid dependence in the USA, after being approved for the treatment of alcohol dependence in 2006. The intramuscular suspension is administered via injection into the gluteus muscle, alternating sides every 4 weeks. A research-only formulation can be injected subcutaneously. With the latter formulation, a heroin challenge study was conducted where participants were administered a 380 mg dose subcutaneously and then received intravenous heroin at dosages of 0, 6.25, 12.5 or 25 mg in a double-blind design. The suspension provided satisfactory blockade of both self-rated and objective measures (e.g. pupillary diameter) of heroin for between 4 and 5 weeks [26]. Recently, a similar experiment was conducted using the Food and Drug Administration-approved intramuscular suspension at reduced dosages of 75, 150 or 300 mg of naltrexone and using hydromorphone instead of heroin for the challenge tests; 3 mg of hydromorphone was blocked by the 300 mg SRX formulation for 28 days, whereas the lower SRX dosages blocked this challenge for a correspondingly shorter duration [27].

Surgically implanted capsules

The other main type of SRX technology consists of pellets with biodegradable solid polymer surgically inserted or implanted under the skin or fatty tissue with the use of local anaesthetic. The wound is then sealed with one to three sutures, with the wound being inspected after about 1 week. The two formulations of surgically implanted naltrexone that have been used in the majority of controlled studies are an Australian type with release periods as long as 7 months when 30 pellets are inserted [28] and a Russian type with a release period of 2–3 months [29]. Other manufacturers of naltrexone implants exist, but little research has been published on their reliability or production methods (see [30] for an exception to this). Case data support the view that SRX implants releasing naltrexone at or above 1 ng (ml blood)$^{-1}$ will block normal dosages of laboratory-administered heroin, as well as high dosages of illicit heroin [24, 31, 32].

Effect on opioid use

The majority of randomized controlled trials (RCTs) on SRX have shown promising increases in heroin abstinence in the SRX group relative to control subjects, despite diversity in sample composition, study design and cultural settings. Two studies have been conducted of 4 week intramuscular SRX suspensions: an 8 week double-blind study from the USA of a selected sample divided into a high-dosage, low-dosage and placebo [33]; and a 24 week double-blind trial of SRX *vs.* placebo in a sample of Russian heroin users [34]. Both studies found significant increases in the proportion of urine samples negative for heroin use.

On implantable naltrexone, five RCTs will be reviewed here. Three RCTs utilized a 6 month version of the Australian implant. One open-label study randomized to treatment as usual in a Norwegian treatment setting [35], and there was a placebo-controlled, double-dummy design with oral naltrexone in Western Australia [36]; both found significant decreases in heroin use. A Norwegian open-label study randomizing to methadone OMT or naltrexone implant in probationer settings experienced dropout problems, and found similar reductions in opioid use among the patients who remained [37]. Two randomized studies have been conducted in Russia using a Russian naltrexone implant. A 10 week study of $n = 100$ patients ($n = 50$ in the SRX and placebo groups, respectively) who were both amphetamine and heroin dependent found significant reductions in heroin use [29]. A larger study that followed $n = 306$ opioid-dependent patients over 6 months in a three-group, double-dummy design found that a significantly larger proportion of urine samples were opioid negative in the active SRX group compared with both oral naltrexone and placebo [38].

The magnitude of the reduction in opioid use with SRX is typically about 50% at a group level when compared with oral naltrexone or usual-treatment control subjects, although there is considerable individual variation among patients. In summary, sustained release naltrexone seems to succeed in assisting patients in achieving abstinence from opioids. The consistency of this finding despite diversity in study designs, cultural setting and SRX formulation reinforces the impression that the effect of SRXs on heroin use is a clinically robust finding. There are few data regarding the effectiveness of SRX in the treatment of addiction to prescription opioids.

Sustained release naltrexone and heroin-related overdose

The ability of naltrexone to compete against heroin for opioid receptors means that it should provide protection against overdose and death. The RCTs thus far completed have an insufficient number of participants to permit meaningful analyses of mortality rates. A series of registry cohort studies from Western Australia have used samples of several thousand patients; these studies suggest that SRX reduces the number of deaths among heroin users compared with methadone users and oral naltrexone [39–41]. The same open cohort was used for the SRX implant patients in two of these studies. Case reports that have been published of patients 'breaking the naltrexone blockade' with large doses of opioids (e.g. [42]), as well as postmortem cases [43], often do not account for potential confounding factors. Data from Norwegian SRX patients confirm that a minority of patients report 'breakthrough'-like experiences, but that the use of non-opioid illicit drugs makes it difficult to verify which substance induced the experience [32]. The concept of true receptor agonism or 'breakthrough' in the presence of naltrexone also appears

to be inconsistent with case stories of naltrexone blocking large quantities of heroin [24, 32].

An extension of this question is whether death from an overdose of heroin can occur in active SRX patients. Like any pharmacotherapy, the binding of naltrexone at the receptor site is of a competitive type that it is technically possible to outperform using extreme quantities of normal-affinity opioids or high-affinity synthetic opioids, such as fentanyl. In clinical settings, obtaining and self-administering agonists of the right type or quantity would be very difficult; deaths in patients treated with a reliable SRX formulation are thus more likely to be caused by exposure to the many non-opioid mortality sources common in the heroin demographic.

Retention in SRX for heroin users

Ambivalence between remaining in treatment and recommencing heroin use means that heroin users are often tempted to drop out from treatment. Thus, retention in treatment is considered to be a highly important measure of the clinical feasibility of any treatment for heroin addiction, including OMT and SRX. For naltrexone treatment, the inability to retain patients in oral naltrexone regimens has strongly contributed to the reason that oral naltrexone treatment has seen minimal adoption in clinical settings with heroin users [21]. A central clinical advantage of sustained release over oral naltrexone is the reduction in dropout opportunities, e.g. one intramuscular injection every 28th day instead of a tablet every day. In one RCT [33], retention was 62% between the first and second 28 day intramuscular SRX administration. In the Russian study of intramuscular SRX (28 days of naltrexone release), attrition at the end of 6 months of administration of intramuscular SRX administrations was about 50% [34]. This is similar to retention between the first and second administration of 6 month implantable SRX [44]. For patients receiving the 10 week Russian implant, retention was 63% over 6 months among Russian heroin users [38] and 52% in the study of patients with both opioid and amphetamine dependence [29]. Differences in study design and setting, as well as differences in re-administration frequencies and adverse event profile make it difficult to infer beyond the finding that retention rates for SRX are within a clinically acceptable range and tend to be better than their comparison group. Thus, in this respect SRX seems to confirm hopes that it would constitute an improvement over oral naltrexone [21].

Integration with other behavioural interventions

A study from the Johns Hopkins behavioural laboratory found that when entry into a voucher-based workplace system was contingent on acceptance of a monthly intramuscular SRX, compliance and retention were improved when patients could enter the workplace freely *vs.* those who were simply prescribed SRX monthly; 74% of contingency patients accepted all six injections, whereas only 26% of prescription patients did the same [45]. This is consistent with previous findings from contingency management with oral naltrexone [46]. This suggests that the retention in SRX can be greatly improved when combined with behavioural interventions in order to maximize its clinical usefulness.

Sustained release naltrexone administered as part of a planned release from prison is another area of considerable interest, in particular due to the increase in overdose mortality reported in several studies (e.g. [7, 47]). Given that heroin is less available in prison, inmates are more likely to maintain abstinence from heroin, which greatly facilitates naltrexone induction [48]. Several studies on oral naltrexone for opioid-dependent inmate populations concluded with beneficial outcomes when naltrexone was integrated with psychosocial support to enhance external motivation, e.g. work-release programmes and parole including follow-up by criminal justice staff [49–52]. Although treatment attrition was still high in these trials, those who stayed on oral naltrexone were less likely to relapse to heroin and less likely to engage in criminal activity than comparison groups not receiving naltrexone. A recent pilot study suggests that intramuscular SRX is feasible in probationers, with participants displaying reductions in opioid use [53]. This is consistent with findings from a Norwegian OMT–SRX randomized study [37], where heroin abstinence rates were equivalent between the two groups 6 months after release. There is debate regarding the ethical aspects of mandating SRX for heroin users as part of sentencing or parole conditions (e.g. [54]).

Concomitant substance use

Several studies have examined whether SRX also reduces concomitant use of non-opioid illicit drugs. Naltrexone has been known to reduce craving for a number of addictive substances (see elsewhere in this issue), often resulting in a subsequent reduction in substance use. Of the available studies, RCTs with stricter inclusion criteria seem to confirm a change in non-opioid drug use [33, 34]; this effect does not reach significance in studies with less strict inclusion criteria [28, 34, 35]. This indicates that SRX may have an effect on concomitant drug use in heroin users, but less dramatic than the effect seen on heroin consumption; the division along inclusion criteria may also indicate that a reduction in concomitant substance use is more likely to occur in subgroups of heroin users that are prescreened to reduce the incidence of potential confounders.

Somatic and mental health outcomes

A registry cohort study in Australia followed cohorts of both SRX and methadone patients, and found that their rate of mental health-related hospitalization reduced to a similar extent [55]. In a similar study, SRX patients presented with fewer psychiatric hospital admissions after entering SRX [56]. For somatic hospitalizations, overdose admissions were reduced to zero among SRX implant patients in a registry linkage study, and continued to be reduced compared with pre-admission levels for an additional 6 months following the expiry of naltrexone from the SRX implant [39].

Adverse events

Moderate adverse effects, such as nausea, vomiting and muscle twitches, are experienced by heroin users in both SRX and oral naltrexone treatment [22, 57]. The majority of adverse effects are described as mild to moderate [35], and are more likely to occur in active SRX groups than in placebo patients [29, 33, 34]. As SRX releases naltrexone into the bloodstream gradually at concentrations typically in the 1–5 ng ml^{-1} range, the intensity of adverse effects is much reduced compared with oral naltrexone, where blood naltrexone levels can remain at 10–30 ng ml^{-1} for several hours every day following tablet intake. The blockade of endogenous opioids thought to result from treatment with SRX has not been reported to have consequences for the occurrence of mood disorders in any of the RCTs thus far published, even though the majority of them administered instruments to measure depression. While there have been reports of depression in users of oral naltrexone [58, 59], subsequent investigations failed to confirm any effects on mood [60, 61]. Clinicians should perhaps be more concerned that naltrexone blocks the effects of opioid agonist-based analgesics in an accident-prone population, although increasing the dosage or using other types of analgesics will often resolve the problem. It has also been suggested that naltrexone increases the sensitivity of the opioid receptor system, making patients more vulnerable than usual to heroin overdose once SRX is concluded [62]. However, findings from toxicological examinations of heroin-related deaths comparing patients with or without prior naltrexone exposure do not support this hypothesis [63]. In addition, a recent database study found a reduction in deaths among SRX patients during the first months following treatment when compared with oral naltrexone patients [41].

An important difference between SRX and oral naltrexone is the occurrence of site-related adverse events [64]. For implantable SRX, these may appear as mild allergic itching or redness around the implantation site, or infection of the skin, stitching or underlying tissue [65]. These events are reported to occur in 2–5% of patients (e.g. [29, 35]) and usually resolve with symptomatic treatment, but in extreme cases may require removal of the implant. Some patients have cosmetic concerns with the fact that some implantable SRX formulations may take months or years to biodegrade completely [66]. Likewise, recipients of SRX with intramuscular suspension can often experience some site pain, while a few per cent experience more serious site reactions, such as induration and infection.

Hepatic health is sometimes a concern with heroin users, especially for patients recently infected with hepatitis C. There is little evidence that SRX in ordinarily administered doses is hepatotoxic. Intramuscular SRX has been found to be well tolerated in alcohol-dependent patients with hepatic impairment, requiring no dose adjustments [67, 68]. A pilot study of implantable SRX in heroin users found key hepatic indicators such as ALT to improve over the course of treatment [31], and the influence of SRX on indicators in other studies has generally been below levels of clinical significance. A clinical study of 50 SRX implant patients undergoing antiviral therapy for hepatitis C found that 62% were hepatitis C virus negative following completion of hepatitis C virus treatment and 6 months of SRX [69]. Still, caution may be warranted in administering SRX to patients who present with severely reduced hepatic functioning, e.g. those who qualify for an impairment classification corresponding to Child–Pugh grade C.

Pregnancy is a debated topic in SRX research, as with heroin users in general [70–72]. Sustained release naltrexone medication is now available for regular prescription in the USA, and there is an interest among pregnant drug users despite a general lack of knowledge about the effects of SRX on fetal health. While this lack of knowledge is unfortunate from a medical point of view, the risk of return to heroin use upon discontinuation of SRX may be considered an even worse outcome. Historically, the solution most often adopted has been to continue the pharmacotherapies for pregnant heroin users and initiate short- and long-term studies on adverse effects following delivery of the child [73]. Only one case has been reported following this approach, with no adverse effects detected in mother or child [74].

Conclusions

Since a Cochrane review in 2008 [75] concluded that there were too few studies to conduct any meaningful assessment of SRX in the opioid addicted, the amount of research published on SRX has accumulated to the point where this conclusion seems gradually less valid. Sustained release naltrexone is showing promising, consistent effects in supporting the efforts of opioid users to achieve abstinence across different clinical study design and treatment settings. The SRX formulations that have been the subject of the majority of research articles appear to have a

satisfactory rate of consistency in naltrexone release and an acceptable adverse effects profile. The literature on SRX for opioid addiction still requires more studies in order to confirm initial findings on effects. There is a particular need for more knowledge on SRX compared with current standard treatments, the impact on poly-drug dependence, the use of SRX during pregnancy and the combination of SRX with other interventions in order to maximize the impact on recovery.

Competing Interests

The authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request) and declare: no support from any organization for the submitted work; G.K.H. had entered into a contractual arrangement (via the University of Western Australia) with Go Medical Industries (who manufacture the Australian naltrexone implant) to conduct a number of research studies in the previous 3 years; G.K.H. had co-authored with Dr George O'Neil (Director, Go Medical Industries) on a number of previous publications.

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