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Sustained-release naltrexone: novel treatment for opioid dependence

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The devastating costs of opioid abuse and dependence underscore the need for effective treatments for these disorders. At present, several different maintenance medications exist for treating opioid dependence, including methadone, buprenorphine and naltrexone. Of these, naltrexone is the only one that possesses no opioid agonist effects. Instead, naltrexone occupies opioid receptors and prevents or reverses the effects produced by opioid agonists. Despite its clear pharmacologic effectiveness, its clinical effectiveness in treating opioid dependence has been disappointing, primarily due to non-compliance with taking the medication. However, the recent availability of sustained-release formulations of naltrexone has renewed interest in this medication. The present paper describes the development of sustained-release naltrexone formulations and discusses the clinical issues associated with their use in treating opioid dependence.

Keywords: depot, heroin, implant, naltrexone, opioid, sustained release

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1. Introduction

Heroin abuse continues to be a significant problem in the US and globally, as measured by a variety of indicators. For example, treatment admission rates doubled between 1993 and 1999 in roughly half of the US, with a triple increase observed in the West and Northeast. In the US, heroin is most often used by injection, although a shift in use from the intravenous to the intranasal route has occurred in recent years (between 1992 and 2002 injection use decreased from 77 to 62%, while intranasal use increased from 20 to 33% [1]). In addition, emergency department mentions of heroin increased by ~ 50% between 1994 and 2001. In 1996, the economic costs of heroin abuse were estimated at US$21.9 billion [2], highlighting the devastating costs of heroin abuse to both the individual and to society in general.

Data from various sources also suggest that abuse of prescription opioids has risen substantially in the US since the mid-1990s [3]. For example, the National Survey on Drug Use and Health revealed that the initiation of non-medical use of prescription pain relievers has quadrupled, from an incidence of 573,000 in 1990 to 2.5 million in 2002 [4]. Furthermore, the estimated number of new initiates in 2004 to non-medical use of pain relievers (2.4 million) even exceeded that of illicit drugs such as cannabis (2.1 million) and cocaine (1.0 million) [5]. The Monitoring the Future (MTF) survey of high-school students recently showed high rates of non-medical use of prescription medications, especially opioid painkillers, despite an otherwise general decline in the abuse of illicit drugs among this population [6]. The treatment admission rate for prescription opioid abuse increased by 233% between 1993 and 2003, from 6 per 100,000 of the population who are 12 years of age and over to 20 per 100,000. Taken together, these data reveal that abuse of prescription opioids in the US has increased substantially in the last decade, which has resulted in sharp rises in

morbidity and mortality at the local and national levels. These epidemiologic data show the scope and severity of the problem of heroin abuse and non-medical use of prescription opioids and they emphasize the need for studies designed to evaluate potential medications for opioid abuse.

2. Maintenance medications for opioid use

A number of pharmacotherapies are available as accepted treatments for opioid abuse and dependence. These include methadone [7,8], buprenorphine and the buprenorphine/naloxone combination [9] and naltrexone [10,11]. Of these, methadone, an orally administered opioid agonist, was one of the earliest and continues to be the most widely used form of pharmacotherapy maintenance treatment. Buprenorphine and the buprenorphine/naloxone combination are the most recently approved medications in the US for treating opioid dependence. Unlike methadone and buprenorphine, naltrexone is an opioid antagonist and, hence, detoxification of the opioid-dependent person, sometimes using small doses of naltrexone itself to speed the detoxification process, is a prerequisite for naltrexone maintenance [201].

3. Oral naltrexone

3.1 Pharmacology of naltrexone

Naltrexone was synthesized in the 1960s as part of a program to develop antagonist treatments for heroin dependence. It consists of several simple modifications of the basic morphine molecular structure, similar to modifications that have been used to produce other opioid drugs, including buprenorphine and naloxone. Naltrexone is a potent, long-acting, competitive opioid antagonist at the μ, κ and δ opioid receptor subtypes [12] that has been used as a maintenance medication with a recommended daily oral dose of 50 mg [13-15]. The major therapeutic feature of naltrexone pharmacology that makes it useful for the treatment of opioid dependence is that, when occupying receptors, it can completely block the effects of opioid agonists [10,11].

3.2 Clinical experience with oral naltrexone

Although the pharmacologic effectiveness of naltrexone in blocking the actions of opioid agonists is unequivocal, early clinical trials of naltrexone in general populations of opioid-dependent patients were relatively discouraging. Dropout rates were high and few patients completed more than 30 – 60 days of treatment [16-18]. Even in patients who perform well on oral naltrexone, eventual relapse to heroin use is common [19,20]. A recent randomized clinical trial conducted in Iran [21] provides more contemporary evidence for the relative effectiveness of naltrexone versus agonist maintenance in a 24-week comparison between naltrexone (50 mg/day), buprenorphine (5 mg/day) and methadone (50 mg/day). The study enrolled 204 patients who were dependent on illicit intravenous buprenorphine. The rate of treatment completion was 21% in the group assigned to naltrexone compared with 59% on buprenorphine and 84% on methadone. Indeed, recent reviews of the effectiveness of oral naltrexone maintenance for the treatment of opioid dependence concluded that the effectiveness of oral naltrexone was either modest or there was '*insufficient evidence to justify the use of naltrexone in maintenance treatment of opioid addicts*' [22,23].

A major problem that is associated with oral naltrexone therapy is poor medication compliance. This may be attributed to several factors. For example, opioid users are accustomed to self-administering potent reinforcers and the complete absence of opioid-induced reinforcing effects may be unacceptable. In addition, unlike methadone, discontinuation of naltrexone maintenance has no adverse consequences, such as the emergence of opioid withdrawal effects. With methadone or buprenorphine maintenance, the emergence of withdrawal symptoms may serve as a deterrent for discontinuing maintenance therapy, but with naltrexone this deterrent is not present. Furthermore, some studies suggest that naltrexone itself may induce adverse neuropsychiatric and gastrointestinal effects, such as dysphoria, nausea and abdominal discomfort [24-26]. All of these factors may contribute to the poor medication compliance seen with oral naltrexone therapy. Thus, despite its potent opioid antagonist properties, medication non-compliance has been a significant impediment to its adoption as a major treatment for opioid dependence.

Despite this relatively discouraging outlook for oral naltrexone maintenance, clinical trials have suggested greater compliance and effectiveness in several subgroups, including patients receiving family therapy [14], patients who are professionals in jeopardy of losing their licenses [27], patients residing in a supportive family environment where naltrexone compliance is encouraged [28] or patients in the parole and criminal justice systems who are at risk of returning to jail [28-30]. Several recent studies specifically aimed at improving medication compliance have also yielded promising results [31-35]. These studies showed that inclusion of contingency management and/or family or partner involvement produced 6-month treatment retention rates of up to 45%. These studies do suggest potential promise for oral naltrexone maintenance, depending on appropriate environmental circumstances or behavioral interventions.

4. Sustained-release naltrexone preparations

One alternative to an oral naltrexone formula is the injection or surgical insertion of a sustained-release preparation of naltrexone, which removes the burden on patients to take medication daily. Sustained-release preparations have commonly involved the use of compressed naltrexone formulations (e.g., using the Wedgewood implant) or the use of naltrexone combined with a polymer or co-polymer base to allow for the more gradual release of naltrexone over prolonged periods of time. Polymer or co-polymer bases have included, for example, a naltrexone–polylactic acid composite [36]; naltrexone copolymer (90% L-lactic acid and 10% glycolic acid) beads [37];

70% naltrexone base in poly(L-lactic-co-glycolic acid) [38]; naltrexone pamoate linear poly(ortho esters) disk [39]; and polylactide co-glycolide microspheres [40]. More recently, a sustained-release naltrexone implant, using a soft, flexible hydrogel technology, is under Phase I/II development for the treatment of opioid dependence [202].

The concept of a sustained-release preparation of naltrexone is not new. Beginning in the mid-1970s, depot formulations of naltrexone were developed and evaluated in laboratory animals [41-46]. These early formulations were mostly abandoned because of wide between-subject variability in plasma concentrations of naltrexone and lack of tissue compatibility.

In 1980, the US National Institutes of Health published information on the necessary/desirable characteristics for naltrexone sustained-release parenteral drug delivery systems. In addition to the ability to provide therapeutically relevant blood naltrexone levels, they noted that products should be clinically effective, biodegradable, have no adverse tissue reaction (i.e., are biocompatible) and should be easy to administer [47,48].

4.1 Sustaining therapeutic levels

A number of clinical reports and studies have provided *prima facie* evidence on the efficacy of sustained preparations to antagonize the actions of heroin. These have reported serum naltrexone levels of 2.8 ng/ml delivered by implant naltrexone as being effective in blocking 500 mg of snorted pure pharmaceutical diamorphine [49], serum naltrexone levels of ~ 2 ng/ml [50-52] as being effective in blocking the effects of 25 mg intravenously administered heroin and plasma levels of ~ 1 ng/ml as being capable of antagonizing the effects of morphine 15 mg [53]. Most authorities now agree that the therapeutic blood level that is required to treat heroin dependence is above 2 ng/ml [54-56]. As yet, most sustained-release naltrexone formulations have been shown to maintain therapeutic blood levels of naltrexone for at least 4 – 8 weeks, if not longer.

4.2 Biodegradability

It has been known for more than two decades that polymers based on lactide isomers are biodegraded by hydrolysis and, even when incorporated with other polymers, are absorbed by the body without adverse reactions [57]. In rats, D,L-lactide/glycolide copolymer microspheres have been shown to be biodegradable, with the vast majority of microsphere degradation occurring by day 150 [58]. In humans, poly-(D,L)-lactide in surgical sutures and screws is reabsorbed by the body through natural pathways [59]. Similarly, following injection into the body, the polylactide co-glycolide hydrolyzes to lactic and glycolic acids, which are further metabolized into carbon dioxide and water [60]. This suggests that polymers based on lactide isomers that have been and are being developed as part of naltrexone sustained-release preparations are likely to be biodegraded.

In vitro and *in vivo* studies indicate that total time to biodegradation may be commensurate with the size of implant mass used, with, for example, a large quantity of poly-(D,L)-lactide degrading over a longer time period than a smaller quantity [61,62]. The time to total biodegradation should not be an issue as long as good tissue compatibility is achieved.

4.3 Tissue compatibility

Despite showing promising naltrexone release patterns and being of 'likely biodegradable materials,' a number of polymers or co-polymers have shown varying therapeutic success. For example, Chiang and colleagues conducted one of the early studies of sustained-release naltrexone in normal, healthy volunteers implanted subcutaneously with naltrexone copolymer (90% L-lactic acid and 10% glycolic acid) beads [37]. Following an initial burst of release, this formulation yielded relatively constant plasma levels of naltrexone (0.3 – 0.5 ng/ml) for up to 1 month. However, when these investigators administered challenge doses of morphine (15 mg i.m.), the results were variable. In some participants, morphine was completely ineffective, while, in others, morphine-like effects were observed. However, perhaps more importantly, data have suggested that this naltrexone preparation had unacceptable levels of biocompatibility, with two of the three human subjects implanted with the naltrexone copolymer (90% L-lactic acid and 10% glycolic acid) beads having them removed at ~ 3 to 4 weeks due to marked inflammatory reactions or other local tissue irritation. Chiang concluded that this result '*may preclude the clinical use of this particular preparation of beads*' [37]. Undoubtedly, comprehensive acceptability of sustained-release naltrexone products as a conventional treatment for opioid dependence is limited by studies showing an acceptable level of tissue reactivity in patients treated with sustained-release preparations.

4.4 Newer formulations

Newer formulations of sustained-release naltrexone have provided more promising results. For example, injectable formulations of naltrexone, such as those produced by Biotek, Inc. (Depotrex® [56,63]), Elbion NV (Naltrel™; originated from DrugAbuse Sciences [64-66]) and Alkermes, Inc. (Vivitrol® [40,67]) seem to produce clinically relevant plasma concentrations of naltrexone, both within and between subjects and a much lower and perhaps clinically acceptable incidences of tissue reactivity.

An injectable, depot formulation of naltrexone (Depotrex) 192 mg or naltrexone base 384 mg per 2.4 or 4.8 ml of solution, respectively, administered intramuscularly into the buttocks antagonized the effects of intravenously administered heroin (0 – 25 mg) for 3 – 5 weeks, depending on the naltrexone dose [56,68]. These studies demonstrated that Depotrex was safe, effective and well tolerated in opioid abusers who were not seeking treatment for their drug use. A subsequent proof-of-concept, placebo-controlled clinical

trial of Depotrex in treatment-seeking heroin abusers showed a robust, dose-related increase in treatment retention, supporting the use of depot naltrexone as a therapeutic strategy for opioid dependence [69].

Vivitrol (formerly known as Vivitrex®; Alkermes, Inc.) is an injectable (subcutaneous or intramuscular) formulation of depot naltrexone encapsulated into polylactide co-glycolide polymer microspheres (~ 100 µm in diameter). Data from studies with rats administered a single (subcutaneous or intramuscular) injection (50 mg/kg) indicate that it produces peak naltrexone plasma levels within 3 days (15 ± 1.4 and 19 ± 3.6 ng/ml, respectively), dropping to undetectable levels (< 1 ng/ml) by 35 days [40]. Similar results have been reported in alcohol-dependent patients, with naltrexone (400 mg i.m.) maintained at presumed therapeutic levels for a full month [203,204]. In rats, these levels were capable of antagonizing the effects of morphine on a hot-plate test over a 4-week period [40]. A sequential intramuscular injection on day 34 produced a similar effect to the initial injection, suppressing morphine-induced analgesia up to day 68 [40]. This polymer is known to readily hydrolyse to lactic and glycolic acid, which is further metabolized into carbon dioxide and water [60]. Preliminary data indicate that, in humans, Vivitrol (naltrexone 380 mg in ~ 5 ml of solution administered intramuscularly into the buttocks) is generally safe and well tolerated and reported adverse effects are mild to moderate. Although over 10% of alcohol-dependent persons experienced some form of adverse event following Vivitrol treatment (nausea, headache, loss of appetite and fatigue), < 2% of patients discontinued treatment because of injection site reactions (induration and angiedema) [205]. With the exception of injection site reactions, reported common adverse effects with Vivitrol are similar to those seen with oral naltrexone formulations [67]. A 12-month extension trial of alcohol-dependent persons found the most common adverse effects to be headache, nasopharyngitis and respiratory tract infections (Alkermes, Inc. press release 2005, 23 May).

More recently, a poly-D,L-lactide implantable formulation of naltrexone has been developed that may provide even longer-lasting blockade of opioid receptors. The naltrexone implant (O'Neil Implant) developed by GoMedical Industries Pty Ltd has shown promise to deliver naltrexone at clinically relevant blood levels above 2 ng/ml for 5 to 6 months [70,71]. This implant is a diffusion-based delivery system, designed such that pockets of naltrexone are isolated by a polymer matrix (a diameter of 100 µm poly-D,L-lactide) to ensure a more gradual release of the naltrexone as the fluid enters the core. A total of 10 – 30 tablets (each tablet measures ~ 8 mm in diameter and 5 mm in height) containing a total of 1.1 g (10 tablets) to 3.3 g (30 tablets) of naltrexone are implanted subcutaneously into the lower abdominal area at each dose administration. Human *in vitro* assessment of tissue samples (biopsies) from 54 patients (34 males) at various periods of time post-implant have shown an early phase (up to 12 months post-implant) of inflammation, foreign body reaction and fibrosis, which gradually settled over the next 12 months until the tissue returned to normal by 25+ months [72]. Additional data from an ultrasound study on 71 heroin-dependent persons treated with this implant have concluded that there was a total absence of the poly(D,L-lactide) implant matrix by an average of 1201 days (Hulse *et al.*, in preparation).

The sustained-release preparations described above are yet to be registered by regulatory authorities for therapeutic use in the management of opioid dependence, although Vivitrol was approved in 2006 by the FDA for the management of alcohol dependence.

4.5 Mode of administration: sustained-release preparation

The mode of administration and its acceptability to substance abuse practitioners and/or patients may prove to be a major consideration in selecting the type of sustained-release product to use in the treatment of opioid dependence. So far, sustained-release preparations of naltrexone have focused on intramuscular or subcutaneous injection or surgical insertion.

Depot preparations have an advantage in that they are relatively easily administered by intramuscular or subcutaneous injection (e.g., Vivitrol and Depotrex), compared with implants (e.g., Wedgewood, Valera, GoMedical), which are commonly inserted surgically under local anesthesia through a small subcutaneous incision. Clearly, some additional physician training may be required to administer naltrexone implants compared with injectable depot preparations. Additionally, patients may have a preference for a depot injection rather than being subjected to a more invasive procedure such as is required for implant treatment.

However, there are a number of additional clinical considerations that may outweigh this and favor implant treatment among community treatment programs for heroin dependence. First, although tissue compatibility is generally good with the more recent formulations of injectable, sustained-release naltrexone, some significant events (e.g., induration, edema, erythema and pruritis progressing to secondary infection requiring surgical debridement and wound care) have been found in a very small proportion of patients. In these instances where removal of polymeric materials is deemed clinically desirable, this may be achieved more readily with an implant than an injectable depot preparation; the latter proving almost impossible to remove, short of excising a large area of tissue. On the other hand, the fact that the implants can be removed surgically raises the possibility that some patients may also attempt to extract the implants from their bodies.

Second, and perhaps more importantly, depot preparations generally provide a shorter period of coverage (1 – 2 months) compared with implants (3 – 6 months). It is difficult to estimate the length of naltrexone antagonist treatment that is required to facilitate significant movement of a previously heroin-dependent person away from the narcotic network and towards mainstream community involvement, but the

provision of an enforced abstinence period of longer duration is likely to be a significant factor in assisting the formerly dependent heroin user to separate from heroin use and the narcotic network and to commence reintegration with the broader community.

Although the initial use of an implantable preparation that provides several months, rather than a few weeks, of coverage may be desirable: the more stable patients may opt to receive a depot preparation rather than once again undergoing the more invasive minor surgery associated with implant treatment. In this respect, different sustained-release preparations may be used sequentially as part of the same management program.

4.6 Poly-drug use

Poly-drug use is commonly observed among heroin-dependent individuals [73-75]. Although naltrexone may provide antagonism against opioids, one concern is that other drug use may replace opioid use, posing a new risk situation for both dependence and risk of overdose. So far, clinical studies on depot [69] and implant naltrexone [76] have indicated that other drug use remained relatively low. This is consistent with findings from other studies reporting on patients entering oral naltrexone maintenance [19,20,77]. Notwithstanding these results, programs offering sustained-release antagonist treatment for opioid dependence should have an enhanced emphasis on preventing, detecting and managing poly-substance use. This approach would also help to protect the small percentage of people who may either continue with or move to other drug use when naltrexone blocks opioid use.

4.7 Accidental opioid overdose following treatment cessation

It has been suggested that the risk of accidental overdose increases after cessation of chronic treatment with naltrexone, either via loss of opioid tolerance or increased sensitivity to opioid agonist administration [78-80]. Support for the notion of increased sensitivity comes from numerous studies conducted in laboratory animals demonstrating an upregulation in μ-opioid receptors following discontinuation of chronic treatment with opioid antagonists [81-89]. There have also been reports of increased opioid overdose in patients following discontinuation of oral naltrexone maintenance, compared with discontinuation of agonist replacement therapies [90,91]. However, in normal human participants a laboratory study of morphine sensitivity before and after naltrexone treatment has failed to show any evidence of μ-receptor upregulation in the respiratory control system, which is the most likely site of opioid overdose lethality [92]. The clinical trial of injectable, sustained-release naltrexone also did not show an increased incidence of opioid overdose [56]. In fact, two studies demonstrated that the incidence of opioid overdoses dramatically decreased in individuals treated with an implantable form of naltrexone [76,93]. It is possible that the gradual dissipation of naltrexone from these sustained-release formulations protected these patients from experiencing opioid overdose.

However, deaths associated with naltrexone implants have been reported [94]. A review of Australia's National Coroners Information System records between the years 2000 and 2004 using the keyword 'naltrexone' revealed that 5 deaths were potentially associated with the naltrexone implant. Of these, naltrexone levels were detected in two cases and were not measured in the other three cases. One male individual, with naltrexone blood concentrations of 300 ng/ml also showed toxic levels of heroin. This is the only case that seems to suggest that the patient died while attempting to overcome the blockade conferred by naltrexone. The other four individuals presumably died of overdoses from multiple drugs (e.g., different combinations of heroin, alcohol, diazepam and/or amfetamine). In the three individuals for whom naltrexone levels were not measured, the naltrexone implant had been removed for unknown reasons 2 weeks prior to death (1 case) or the naltrexone implant had been administered 6 months prior to death (2 cases). Therefore, in these latter cases, it is likely that insufficient levels of naltrexone were in the body to antagonize the effects of opioid agonists. This report emphasizes the need to caution patients about the risks of opioid and other drug overdose both during treatment with naltrexone and during the period of expected dissipation of naltrexone.

4.8 Liver toxicity

Another potential safety issue that is associated with the long-term use of naltrexone is liver toxicity. This issue has warranted close attention in light of the high rate of hepatitis in intravenous drug users as well as the possibility of hepatocellular injury described in the package insert for oral naltrexone. As yet, several studies have demonstrated that transaminase levels do not change significantly, even after daily administration of high doses of naltrexone (100 – 350 mg) [95-97]. Alcoholic patients who are treated with naltrexone have actually shown liver enzyme decreases, presumably because they are drinking less alcohol [63,98]. Depot naltrexone has also been shown to have minimal effects on liver functioning in heroin-dependent individuals [56]. Elevated liver enzymes typically occur only at doses above 300 mg/day when naltrexone is administered for several weeks; the elevation is a dose- and time-related phenomenon. It is reversible if the dose is lowered or if the medication is discontinued. As a result, liver enzyme monitoring is prudent during treatment with naltrexone and guidelines generally suggest that it should not be administered in patients with advanced liver disease [99].

4.9 Neuroendocrine dysregulation

There has been concern raised that opioid antagonists such as naltrexone may aggravate neuroendocrine dysregulation underlying opioid dependence [100]. However, more research is needed to determine the extent of this concern clinically, as well as a broader effort to determine predictors of which patients are more or less likely to have a successful treatment outcome with naltrexone.

4.10 Pain management

Patients who are being treated with naltrexone should carry an identification card indicating this in their wallet or a medical alert bracelet. In the event of serious injury or the need for treatment of severe acute pain or surgery, treating physicians will need to be aware that higher doses of opioid analgesics may be needed. In addition, the appropriateness of managing pain with non-opioids such as NSAIDs or local anesthesia should be considered. The most effective methods for managing pain in this scenario have not been described clearly in the literature.

5. Expert opinion and conclusions

Despite the promise of sustained-release preparations to maintain therapeutic levels of naltrexone for significant periods, it should be emphasized that management with sustained-release formulations of naltrexone simply creates a window to facilitate movement of the previously opioid-dependent patient away from the narcotic network and back into the general community. The role of psychosocial auxiliary services as part of a treatment package to manage this transition should not be underestimated. Failure to provide adequate psychotherapy to facilitate a heroin-free lifestyle after treatment with sustained-release naltrexone will undoubtedly yield a greater incidence of adverse events and relapse back to dependent heroin use.

In summary, the availability of biocompatible and biodegradable naltrexone preparations that provide long-lasting antagonism of opioid agonist effects represents an exciting new development in the treatment of opioid dependence. Some of the potential risks associated with the use of sustained-release naltrexone for treating opioid dependence that have not been fully characterized are: the increased use of opioids in an attempt to overcome the blockade; the increased use of other drugs of abuse; and inadequate pain relief when treatment with opioids is indicated. Thus far, there is little evidence that opioid overdose is a serious risk that is associated with long-lasting formulations of naltrexone and preliminary evidence suggests that abuse of other drugs actually declines, rather than increases, in opioid-abusing patients treated with naltrexone. With regards to pain relief, non-opioid treatment options are available, but the most effective ways of managing pain in this setting have yet to be determined. This issue is particularly pertinent with the use of injectable formulations of naltrexone because they cannot be removed easily. It is clear that much work remains to be performed to fully characterize the potential risks that are associated with this form of treatment, but initial research suggests that it is a highly promising, safe and effective treatment strategy for opioid dependence. Future research will determine how the clinical effectiveness of sustained-release naltrexone compares to opioid agonist maintenance therapy.

Disclosure

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