

Improving Clinical Outcomes in Treating Heroin Dependence

Randomized, Controlled Trial of Oral or Implant Naltrexone

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Context: Oral naltrexone hydrochloride effectively antagonizes heroin, but its utility is limited by patient non-compliance. Sustained-release preparations may overcome this limitation.

Objective: To compare the safety and efficacy of a single-treatment sustained-release naltrexone implant with daily oral naltrexone treatment.

Design: Seventy heroin-dependent volunteers entered a randomized, double-blind, double-placebo controlled trial with a 6-month follow-up period.

Patients: Eligibility criteria were *DSM-IV* opioid (heroin) dependence; age 18 years or older; willingness to be randomized; residing in the Perth, Western Australia, metropolitan area; and completion of preclinical screening and written consent. A total of 129 eligible participants were identified, and 70 (54%) provided informed consent and were randomized as per the study design.

Intervention: Participants received oral naltrexone, 50 mg/d, for 6 months (plus placebo implants) or a single dose of 2.3 g of naltrexone implant (plus placebo tablets).

Main Outcome Measures: (1) Maintaining therapeutic naltrexone levels above 2 ng/mL; (2) return to regular heroin use (≥ 4 d/wk); (3) other heroin use and ab-

stinence; (4) use of illicit nonopioid drugs; (5) number of opiate overdoses requiring hospitalization; (6) treatment-related unexpected and expected adverse events; and (7) blood naltrexone levels (ie, pharmacokinetic profile) for recipients of active naltrexone implants.

Results: More participants in the oral vs the implant group had blood naltrexone levels below 2 ng/mL in months 1 ($P < .001$) and 2 ($P = .01$); in addition, more oral group participants had returned to regular heroin use by 6 months ($P = .003$) and at an earlier stage (median [SE], 115 [12.0] days vs 158 [9.4] days). There were 10 trial-related, unexpected adverse events. One serious adverse event, a wound hematoma, was associated with surgical implantation. Naltrexone blood levels in implant recipients were maintained above 1 and 2 ng/mL for 101 (95% confidence interval, 83-119) and 56 (39-73) days, respectively, among men and 124 (88-175) and 43 (16-79) days among women.

Conclusions: The naltrexone implant effectively reduced relapse to regular heroin use compared with oral naltrexone and was not associated with major adverse events.

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THE EFFECTIVENESS OF NALTREXONE hydrochloride in antagonizing the objective and subjective effects of heroin is well established.¹⁻⁴

However, although the US Food and Drug Administration approved the use of oral naltrexone to treat opiate dependence in 1984, the clinical efficacy in treating opioid dependence has been limited, primarily because of patient noncompliance with daily oral dosing regimens.^{5,6}

One alternative to oral naltrexone is the injection or surgical insertion of sustained-release preparations, which removes the onus on patients to consume daily medication.

Sustained-release preparations have commonly involved compressed naltrexone or naltrexone/polymer/copolymer base formulations administered subcutaneously or intramuscularly and have been shown to maintain therapeutic blood levels of above 1- to 2-ng/mL naltrexone for 4 to 6 weeks.⁶ One randomized study compared a 30-day injectable naltrexone formulation with placebo for 60 days and concluded that the formulation was safe and effective in increasing rates of opioid-free urine samples.⁷ However, to our knowledge, no sustained-release formulation has been systematically evaluated in comparison with oral naltrexone in treating heroin dependence.

Despite addressing issues of daily oral naltrexone non-compliance, these sustained-release formulations still rely on patients returning monthly for subsequent treatments over several months, and failure to return for subsequent treatment remains a potential problem. For example, when treated with a 30-day injectable naltrexone formulation of either 192 or 384 mg of naltrexone, 40% and 32% of patients, respectively, failed to return for subsequent treatment by month 2.⁷ Therefore, treatment with longer-acting preparations that reduces the frequency of subsequent treatments is more desirable.

Recently, a poly(D,L-lactide) implantable formulation of naltrexone has been developed and has shown promise by delivering naltrexone at clinically relevant blood levels above 1 to 2 ng/mL for 95 to 145 days, depending on the implant dose.⁸ Human in vitro assessment indicates acceptable tissue reactivity and biodegradability.^{9,10}

This study aimed to assess, using a randomized, double-blind, placebo-controlled design, the safety and efficacy of a long-acting sustained-release naltrexone implant compared with the standard oral naltrexone formula.

METHODS

OBJECTIVES AND OUTCOMES

Using a randomized, double-blind, double-placebo controlled design, we compared the safety and effectiveness of naltrexone implants with oral naltrexone to treat heroin dependence for 6 months.

The primary outcomes were (1) maintenance of therapeutic blood naltrexone levels; (2) return to regular heroin use (≥ 4 d/wk); (3) other heroin use and abstinence (self-report with and without verification by urinalysis); (4) use of illicit nonopioid drugs; (5) number of opiate overdoses requiring hospitalization; (6) treatment-related unexpected and expected adverse events; and (7) blood naltrexone levels (ie, pharmacokinetic profile) for recipients of active naltrexone implants.

PARTICIPANTS

Participants were recruited via newspaper advertisements and by referral from community physicians, hospitals, and treatment centers. Eligibility criteria were *DSM-IV* opioid (heroin) dependence; age 18 years or older; willingness to be randomized; residing in the Perth, Western Australia, metropolitan area; and completion of preclinical screening and written consent. Exclusion criteria were 3 or more opioid overdoses in the past month; subsequent treatment with oral naltrexone more than 4 times in the previous 3 months; previous sustained-release naltrexone treatment; concurrent enrollment in other opioid dependence research; pregnancy; active skin or other infections that would increase the risk of infection at the implantation site; contraindications to naltrexone, eg, chronic hepatitis with associated liver damage and/or disease or a medical condition requiring narcotic treatment, such as management of pain; history of an adverse reaction to treatment medications; or inability to complete the study protocol, eg, plans to relocate. Eligibility was determined via a self-reported screening questionnaire and a medical examination. Initial treatment and follow-up took place at a community-based not-for-profit substance treatment center located in the Perth metropolitan area. All patients were encouraged to attend weekly individual, group, or family therapy.

At the end of the trial or at the time of withdrawal, participants were offered a choice of treatments or referral to an alternative treatment provider.

STUDY DESIGN

The present study design ensured that all participants received treatment with either oral or implant naltrexone while also receiving a placebo implant or tablet, respectively. No double-placebo control was considered, in accord with guidelines set out by the Australian National Health and Medical Research Council, which prohibits use of a placebo control when there is already an existing treatment or risk of harm in the absence of treatment.¹¹

IMPLANTS

Active and placebo naltrexone implants (O'Neil implant; Go Medical Inc, Subiaco, Australia) were manufactured in accord with the Australian Code of Good Manufacturing Practice (GMP) and were purchased by the researchers with competitive research funds. Active naltrexone implants incorporated naltrexone-loaded poly-[trans-3,6-dimethyl-1,4-dioxane-2,5-dione] (D,L-lactide) microspheres compressed into tablets with a poly (D,L-lactide) coating, as described previously.⁸⁻¹⁰ Batch data indicate that each tablet weighed 317 mg, with a 37% (117 mg) naltrexone loading and an expected in vitro release rate of 0.6% residual mass per day. Each treatment involved 20 naltrexone tablets containing a total of approximately 2.3 g of naltrexone. The 20 naltrexone tablets were prepacked in three 2-mL syringes with bevelled ends for subcutaneous insertion. This study is the first, to our knowledge, to report on these implants manufactured under GMP conditions. The same formulation has previously been manufactured in a university clinical pharmacology laboratory setting, and estimates indicate that the implants maintain blood naltrexone levels at or above 2 ng/mL for as long as 136 days,⁸ or 5.5 months, when standardized to a 70-kg person.¹²

MASKING

Syringes were opaque to mask the difference in color between active (yellow) and placebo (white) tablets. Active implants were packed with a placebo tablet at the front and rear to ensure that the type of implant could not be discerned during the insertion procedure. Placebo implant tablets were made of blank polymer microspheres compressed into tablets.

Active oral naltrexone tablets (50 mg of naltrexone hydrochloride; Orphan Australia, Berwick) were combined with directly compressible lactose and packed into a solid, white, size-0 gelatin capsule (average mass, 548 mg). Placebo capsules consisted of directly compressible lactose in identical capsules (average mass, 698 mg). Stability and dissolution times for the encapsulated oral formulation were confirmed by the GMP-accredited supplier (IDT, Australia Limited, Boronia).

RANDOMIZATION AND CONCEALMENT

Randomization codes were generated by computer with a variable block size and a 1:1 allocation ratio. Packs (active implant plus placebo tablets or placebo implant plus active tablets) were labeled with these codes. Personnel generating the codes and handling the research medications did not have contact with participants. Study research officers undertaking assessment, recruitment, and patient follow-up had no access to the codes.

All participants underwent detoxification by a standard clinical protocol,¹³ which was conducted as an outpatient procedure. To minimize the adverse effects of opiate withdrawal, participants were advised not to use opioids on the day of the procedure and to reduce consumption in the preceding days. Implant treatment involved a minor operation and local anesthetic with the subcutaneous insertion of implants into the side of the lower abdomen and was conducted on the same day as the detoxification procedure (day 0).¹² A bottle containing 30 capsules (placebo or naltrexone) was dispensed to participants on day 1 and then every 28 days until day 168 (6 months). A non-drug-using, salient person, such as a family member or partner, was enlisted to supervise and encourage daily use of the oral formula.

BASELINE DATA

For both groups, initial demographic data were collected on sex, age, body weight, and Opiate Treatment Index Social Functioning and General Health Questionnaire 28 score.¹⁴ Routine follow-up was scheduled on days 1, 5, 8, 15, and 28 and then every 14 to 168 days. Examination of the surgical incision site and site of implantation was on days 1, 5, 8, and 14 and then every 28 days. Self-reported data on opioid and other drug use, adverse events, opioid or other drug overdose, and any other substance use treatment were collected at baseline and then every 28 days. Blood samples for naltrexone quantification were scheduled at baseline; on days 1, 5, and 28; and then every 28 days and were analyzed at the State Chemistry Centre (Curtin University, Bentley, Western Australia) using liquid chromatography–mass spectrometry.¹⁵ Unsupervised urine drug screenings were scheduled at baseline and on day 15 and then every 28 days.

DEFINITIONS AND STATISTICAL METHODS

The primary end points were the proportion of participants with blood naltrexone levels at or above therapeutic levels (results reported for 0.00–0.99, 1.00–1.99, and ≥ 2 ng/mL) at each monthly blood test and the number of opiate overdoses requiring hospital (including emergency department) treatment. The sample size was based on an estimate that 60% of oral and 90% of implant group participants would have therapeutic blood levels of naltrexone at 6 months (32 per group; power, 80%; $\alpha < .05$). Missing blood naltrexone levels were classified as 0. For participants who withdrew from the trial and received non-study treatment via a second implant or additional oral naltrexone but who continued to provide blood samples, subsequent data were excluded in estimating the pharmacokinetic blood naltrexone profile provided by the single treatment implant. Drug-related analyses used an intention-to-treat approach.

Differences in proportions were assessed with Fisher exact tests, and continuous variables were compared with *t* tests or Mann-Whitney tests, as appropriate. Hazard ratios for drug-related outcomes were computed via Cox proportional hazards regression models with age, sex, years of regular heroin use, body mass index (calculated as weight in kilograms divided by height in meters squared), and group as covariates. Time to return to heroin use 4 or more days per week or unavailable for follow-up was evaluated with Kaplan-Meier survival analysis and log-rank tests. For exponential blood naltrexone modeling, missing blood data were not included in the analysis. Naltrexone readings of 0 were converted to 0.1 ng/mL, consistent with previous practice.⁸

The University of Western Australia Human Research Ethics Committee approved the study protocol. The study was overseen by an independent monitoring committee (IMC) consisting of 4 senior physicians experienced in morbidities associated with the study population and clinical trial monitoring. The IMC was given administrative support by a research officer and met quarterly, with other contacts as required. All adverse events identified during clinical or study contacts were reported to the IMC before unbinding of the treatment allocation. The IMC used the Therapeutic Goods Administration algorithm and guidelines to classify events as serious adverse events (leading to hospitalization or life threatening) or adverse events. The Therapeutic Goods Administration guidelines^{16,17} are based on the relevant International Conference on Harmonisation policies. The principal investigator (G.K.H.) was required to provide quarterly reports to the Commonwealth Department of Health describing the progress of the study and adverse events. Study-related unexpected and expected adverse events as well as serious adverse events are reported in the “Results” section. Data collected were audited for Good Clinical Practice compliance by an independent study monitor and were double-entered with computerized verification.

RESULTS

Recruitment commenced January 17, 2006, and was completed January 31, 2007, with follow-up of 6 months' duration. A CONSORT (Consolidated Standards of Reporting Trials) diagram shows the flow of participants through the study (**Figure 1**). A total of 236 people were screened, and 107 (45%) did not meet selection criteria. Of the remaining 129 eligible to participate, 59 (46%) declined, and 70 (54%) enrolled.

The baseline characteristics of those randomized to oral or implant naltrexone were not significantly different (**Table 1**).

FOLLOW-UP

The oral group attended significantly fewer clinical and research follow-up visits than the implant group (median [interquartile range], 10 [7–13] vs 13 [8–15]; $P = .02$). Six participants (2 of 34 in the oral group and 4 of 35 in the implant group) withdrew from the study between days 2 and 50 without heroin use; 4 stayed in contact with the clinic and 2 were subsequently unavailable for follow-up. Overall, 5 oral naltrexone and 4 implant group participants were unavailable for follow-up. In addition, 1 participant in the naltrexone implant group was subsequently diagnosed as having active methicillin-resistant *Staphylococcus aureus* infection. Based on medical advice, this participant withdrew from the study, had the implant removed, and then was switched to oral naltrexone treatment. Thirteen oral and 2 implant group participants engaged in high-risk heroin use, defined as a return to daily heroin use, commonly involving the use of multiple drugs, in which, in the assessment of the treating physician, the risk of accidental overdose and possible associated morbidity or mortality was significant. Their trial participation was discontinued, and an alternative treatment was offered (Figure 1).

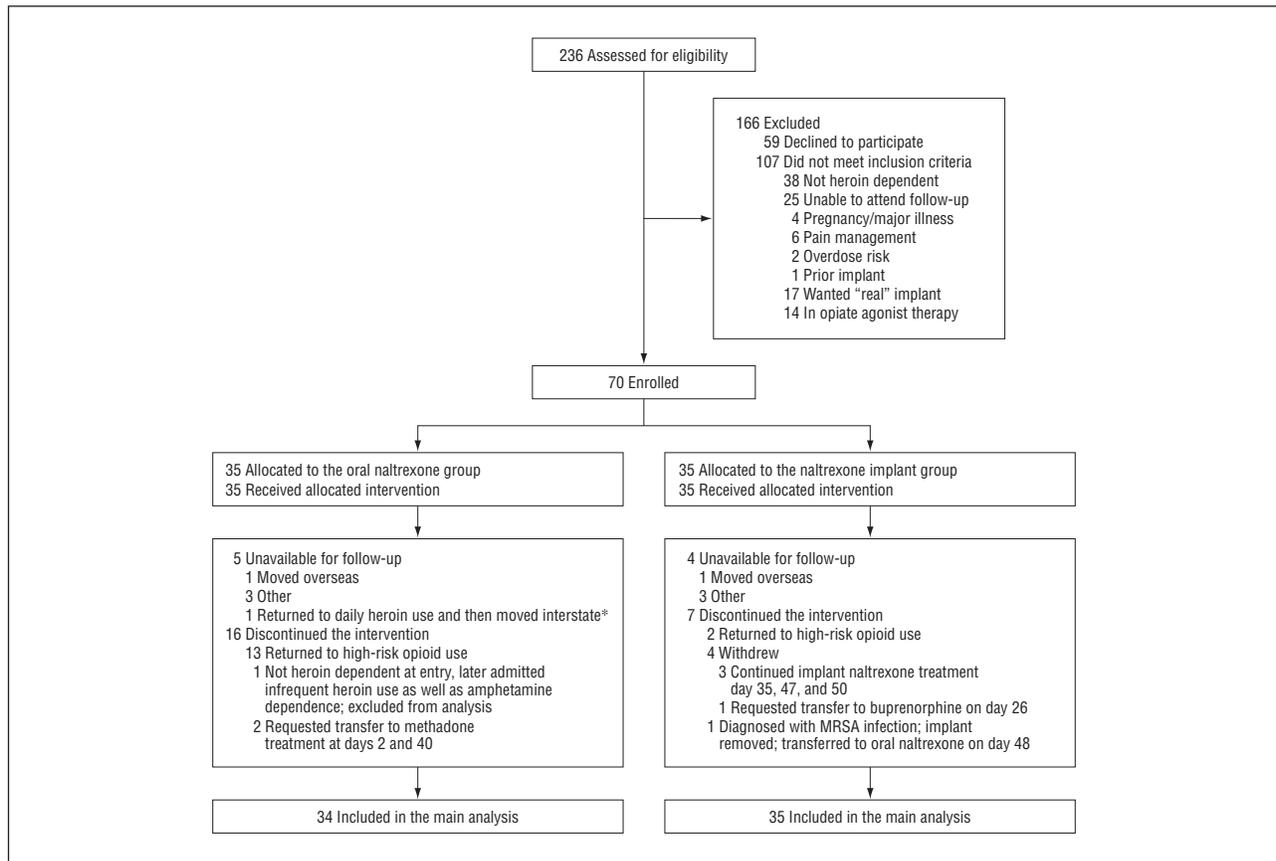


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. Asterisk indicates that the participant was classified as having returned to daily heroin use in analyses; MRSA, methicillin-resistant *Staphylococcus aureus*.

BLOOD NALTREXONE LEVEL

Significantly more participants in the oral vs the implant naltrexone group had blood naltrexone levels of less than 2 ng/mL at months 1 and 2, and significantly more participants in the oral naltrexone group had blood naltrexone levels below 1 ng/mL at months 1 through 4 (**Table 2**). We obtained 193 blood samples from naltrexone implant recipients; 3 participants with only 1 available sample were excluded. From these samples, it was estimated that the period for which blood naltrexone concentration was maintained above 2 ng/mL and 1 ng/mL for men (mean body mass index, 25.5; age, 33 years) was 56 (95% confidence interval [CI], 39-73) and 101 (83-119) days, respectively. The corresponding estimates for women (mean body mass index, 25.1; age, 28 years) were 43 (95% CI, 16-79) and 124 (88-175) days, respectively.

RETURN TO HEROIN USE

Overall, significantly more participants in the oral naltrexone group returned to regular heroin use by 6 months (hazard ratio, 4.49; 95% CI, 1.85-10.90). **Table 3** shows end points for regular (≥ 4 d/wk) heroin use, other levels of heroin use, abstinence (validated and not validated by urine drug screening), and nonopioid drug use.

Survival curves for return to regular heroin use or loss to follow-up indicate that return to regular heroin use

Table 1. Baseline Demographic Characteristics for the Randomized Groups^a

Variable	Implant Naltrexone Group (n=35)	Oral Naltrexone Group (n=34)	P Value
Men, No. (%)	22 (63)	22 (65)	>.99
Age, y	30.9 (8.5)	30.9 (8.5)	>.99
Age at first heroin use, y	19.9 (5.5)	20.0 (6.2)	.95
Duration of regular heroin use, y	8.4 (6.3)	10.4 (7.3)	.23
BMI ^b	25.0 (6.9)	23.9 (5.0)	.45
DSM-IV total No. of criteria, median (IQR) ^c	7 (6-7)	7 (6-7)	.67
OTI GHQ-28 potential cases, No. (%)	28 (80)	28 (82)	>.99
OTI S-F score ^d	26.9 (13.5)	23.0 (13.7)	.23

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; OTI GHQ-28, Opiate Treatment Index General Health Questionnaire 28 scored using the conventional method, in which a threshold score of 4/5 shows potential cases¹⁸; OTI S-F, Opiate Treatment Index Social Functioning Subscale.

^aData are given as the mean (SD) unless otherwise indicated.

^bCalculated as weight in kilograms divided by height in meters squared.

^cThe total number of criteria met for DSM-IV opioid (heroin) dependence.

^dData were missing for 1 participant.

occurred significantly earlier among participants in the oral group compared with the implant naltrexone group (median [SE], 115 [12.0] vs 158 [9.4] days; $P=.001$) (**Figure 2**).

Table 2. Blood Naltrexone Levels by Month^a

Blood Naltrexone Level, ng/mL	Study Group, No. (%) of Participants		P Value ^a
	Implant Naltrexone	Oral Naltrexone	
Month 1			
0.00-0.99	0 (0)	20 (59)	...
1.00-1.99	2 (6)	4 (12)	< .001 ^b
≥2.00	32 (94)	10 (29)	< .001 ^c
Month 2			
0.00-0.99	6 (18)	23 (74)	...
1.00-1.99	10 (30)	2 (7)	< .001 ^b
≥2.00	17 (52)	6 (19)	.01 ^c
Month 3			
0.00-0.99	16 (53)	25 (80)	...
1.00-1.99	9 (30)	3 (10)	.03 ^b
≥2.00	5 (17)	3 (10)	.47 ^c
Month 4			
0.00-0.99	16 (53)	29 (97)	...
1.00-1.99	8 (27)	0 (0)	< .001 ^b
≥2.00	6 (20)	1 (3)	.10 ^c
Month 5			
0.00-0.99	24 (80)	27 (96)	...
1.00-1.99	4 (13)	0 (0.0)	.10 ^b
≥2.00	2 (7)	1 (4)	> .99 ^c
Month 6			
0.00-0.99	25 (83)	26 (96)	...
1.00-1.99	3 (10)	1 (4)	.20 ^b
≥2.00	2 (7)	0 (0)	.49 ^c

Abbreviation: ellipses, not applicable.

^aSamples collected after participants received additional naltrexone treatment (eg, second implant, supplementary oral naltrexone) were excluded. Assessed with Fisher exact test.

^bAnalysis compared the proportion of participants with blood naltrexone levels of 1.00 ng/mL or greater to the proportion with levels below 1.00 ng/mL.

^cAnalysis compared the proportion of participants with blood naltrexone levels of 2.00 ng/mL or greater to the proportion with levels below 2.00 ng/mL.

In addition, during the 6-month follow-up period, 3 (9%) oral and 2 (6%) implant group participants returned to using heroin 1 to 3 days per week, no participants in the oral and 5 (14%) in the implant group returned to heroin use 1 to 3 days per month, and 9 participants (26%) in the oral and 22 (63%) in the implant group self-reported complete abstinence (Table 3). Among participants who self-reported abstinence, opioid-free status could be validated by urinalysis results negative for opioids for 7 (21%) oral and 17 (49%) implant naltrexone group participants (hazard ratio, 1.77; 95% CI, 0.90-3.28) (Table 3). No opiate overdoses requiring hospital treatment in emergency departments or hospital admission were reported during the 6-month follow-up period.

NONOPIOID DRUG USE

Both treatment groups had similar patterns of use for individual categories of drugs, and overall use of non-opioid drugs was similar between groups (hazard ratio, 0.58; 95% CI, 0.32-1.05). The most frequently reported category of nonopioid drug use was cannabis, with 7 oral and 11 implant group participants reporting daily use. The next most frequently reported category was stimulants, with 1 oral participant and 4 implant group participants reporting daily use.

Table 3. Drug-Related Study End Points and Self-reported Heroin Use^a

End Point	6-mo Intention-to-Treat Analysis, No. (%) of Participants		HR (95% CI)
	Implant Naltrexone Group (n=35)	Oral Naltrexone Group (n=34)	
Self-reported heroin use			
Regular heroin use ^b	6 (17)	21 (62)	5.57 (2.18-14.24) ^c
1-3 d/wk	2 (6)	4 (12)	...
1-3 d/mo	5 (14)	0 (0)	...
Abstinence	22 (63)	9 (26)	...
Self-reported opioid abstinence and urinalysis results validation	17 (49)	7 (21)	1.77 (0.90-3.28)
Self-reported any use of illicit/misuse of licit substances	33 (94)	26 (76)	0.58 (0.32-1.05)

Abbreviations: CI, confidence interval; ellipses, not calculated; HR, hazard ratio.

^aCovariates in the Cox model were sex, baseline age, years of regular heroin use, body mass index, and treatment group.

^bRegular heroin use was defined as 4 or more days per week or unavailable for follow-up.

^cP < .001.

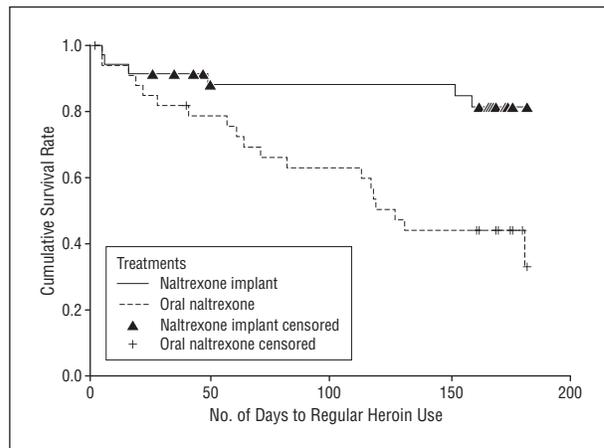


Figure 2. Cumulative survival and number of days until regular heroin use (≥4 d/wk; those unavailable for follow-up treated as return to regular heroin use). Cases were censored at study withdrawal/loss to follow-up or at last contact within 14 days before the end of study (maximum, 182 days).

STUDY-RELATED ADVERSE EVENTS

One participant in the implant group had a severe adverse event that was classified as study related but expected: a wound hematoma (bleeding, swelling, and pain proximal to the implant site) related to the surgical procedure. Ten study-related adverse events, 4 in the oral and 6 in the implant naltrexone group, were classified as unexpected and were typically diarrhea or headache (Table 4). The 29 study-related but expected adverse events, 10 in the oral and 19 in the implant naltrexone group, were typically opiate withdrawal symptoms (eg,

Table 4. Study-Related Expected Serious Adverse Events and Unexpected Adverse Events

Participant ID No.	IMC Category	No. of Days Postrandomization	Description
Oral Naltrexone Group			
28	Unexpected adverse event	28	Depressed
17	Unexpected adverse event	29	Headache
17	Unexpected adverse event	29	Metallic taste in mouth
15	Unexpected adverse event	180	Redness extending to 5 mm from wound site and 10 mm from implant site
Naltrexone Implant Group			
52	Expected serious adverse event	0	Wound hematoma
39	Unexpected adverse event	15	Erectile dysfunction
9	Unexpected adverse event	24	Diarrhea
1	Unexpected adverse event	28	Diarrhea
13	Unexpected adverse event	46, 106, 120, and 149	Abdominal cramps and diarrhea
70	Unexpected adverse event	62	Swelling extending up 10 mm from implant pellets
70	Unexpected adverse event	64	Headache

Abbreviations: ID, identification; IMC, independent monitoring committee.

diarrhea, nausea, vomiting) or exudation, redness, or pain at the surgical incision site or proximal to the implant during the first 14 days after surgery.

COMMENT

The findings of the study support the use of this sustained-release naltrexone implant to improve clinical outcomes during heroin dependence treatment, although the implant provided a shorter duration of therapeutic coverage than anticipated. During a 6-month follow-up period, participants assigned to oral naltrexone were at greater risk of returning to regular heroin use than were implant naltrexone participants. Furthermore, participants treated with oral naltrexone returned to heroin use at an earlier date compared with the implant naltrexone group (median, 115 vs 158 days).

Given the transient and marginal lifestyles of many heroin users, loss of study participants over time is not unexpected (eg, 70% unavailable for follow-up at 3 months¹⁹ and 52% at 12 months²⁰). Data regarding the return to regular heroin use were calculated after following the accepted, rigorous clinical trial assessment procedure of regarding any subject unavailable for follow-up (5 participants in the oral group and 4 in the implant naltrexone group) as having relapsed to regular heroin use. However, from a clinical perspective, among those not available for follow-up, many participants treated with oral naltrexone were observed to return to regular heroin use during the first 130 days of treatment, whereas this was not observed among those treated with implant naltrexone. Only 2 participants in the implant group reported returning to regular heroin use, at 152 and 159 days (Figure 2). Clinically, these results are particularly impressive.

This difference notwithstanding, 14% of participants in the implant naltrexone group reported using heroin 1 to 3 days per month, and a smaller group reported using heroin 1 to 3 days per week. These results contrast with those from the oral naltrexone group, in which no participant maintained heroin use at levels of 1 to 3 days a month and only 4 participants (12%) used heroin 1 to 3

days per week. That is, in most instances in which heroin use occurred, participants treated by oral naltrexone relapsed to regular heroin use, whereas this outcome was not observed among those treated by implant naltrexone. The lower level of use among participants in the naltrexone implant group may be associated with patients using heroin to determine whether they could achieve an opioid effect, with an unsatisfactory outcome resulting in discontinuation of heroin use. Infrequent heroin use among a number of participants in the implant naltrexone group explains why this group showed significantly less return to regular heroin use compared with the oral naltrexone group but not statistically different levels of heroin abstinence when confirmed by opioid-free results of urine drug screening (17 of 35 implant group participants and 7 of 34 oral group participants).

There is some dispute concerning the precise level of naltrexone required to be therapeutically effective in managing heroin dependence, but the 1- to 2-ng/mL range is typically cited.⁶ Naltrexone blood levels among implant group participants were maintained above 1 and 2 ng/mL for 101 and 56 days, respectively, among men and 124 and 43 days among women. Sex differences in the duration of coverage provided by implant naltrexone have previously been identified, with differences in body weight, body fat, percentage of lean muscle, and bone density suggested as potential causes.⁸ Time until return to regular heroin use was consistent with the assertion that the therapeutic blood naltrexone level for the management of heroin dependence is between 1 and 2 ng/mL⁶ and suggests that, in the present study, naltrexone blood levels below 1 ng/mL may be a marker for considering subsequent treatment. However, examples of patients with naltrexone blood levels exceeding 1 ng/mL overriding naltrexone implants with large opioid doses have been reported.^{21,22}

To date, most sustained-release preparations have been shown to maintain therapeutic blood levels of above 1- to 2-ng/mL naltrexone for 4 to 6 weeks.⁶ Given the propensity of heroin-dependent persons not to return for sequential monthly treatment,⁷ the current implant may have an advantage because it reduces the frequency of

subsequent treatments and provides an extended therapeutic period in which the patient can affect significant life changes. However, although this implant formulation may confer a longer duration of coverage than other sustained-release products, a minor surgical procedure is required to insert the implant. Therefore, injectable formulations⁷ may be more acceptable to some patients and health care providers.

Of importance, a large proportion of the implant naltrexone group were abstinent from heroin, and others did not use heroin regularly for 6 months; therefore, single or sequential applications of this type of treatment might significantly affect the long-term prognosis for heroin-dependent persons. The use of sequential implants to maintain therapeutic blood levels for periods of 12 months has been reported previously in an open-treatment cohort.^{23,24} Thus, it is likely that the relapse rate for heroin dependence can be greatly reduced using this approach to treatment.

The time during which naltrexone blood levels were maintained above 1 or 2 ng/mL among implant group participants was shorter than that previously reported for similar implants.^{8,12,25} These earlier studies investigated naltrexone implants developed and produced in a university Department of Clinical Pharmacology, with an *in vitro* release rate of approximately 0.3% to 0.4% of their mass per day^{8,12,25} compared with the present study release rate of 0.6%, and they included reports on implants with greater naltrexone mass. The present study is the first, to our knowledge, to investigate the new O'Neil implant manufactured by Go Medical Inc in a purpose-built facility adhering to the Australian Code of GMP, with batch testing overseen, inspected, and certified by the regulatory authority. The manufacturing modifications required for GMP certification likely resulted in the change in the release rate.

Of 6 unexpected adverse events in the implant naltrexone group, 3 were diarrhea. No participants in the oral naltrexone group had clinically significant diarrhea, although gastrointestinal symptoms are a well-established effect of this treatment.²⁶ Gastrointestinal adverse events, including diarrhea, have previously been reported with other sustained-release naltrexone preparations.²⁷⁻³⁰ These data may flag increased incidents of diarrhea as a clinical feature associated with sustained-release naltrexone. Alternatively, the greater number of clinical and research contacts among implant vs oral group participants during the study period may have increased the reporting of adverse events, including diarrhea, for this group, whereas early cessation or intermittent use of oral naltrexone may have reduced the incidence of adverse events.

One serious adverse event, a wound hematoma, was associated with surgical implantation in an active implant group participant. The participant was admitted to a hospital for an overnight stay, and the condition quickly resolved. Nevertheless, this incident highlights a potential risk associated with subcutaneous surgical insertion of this implant. Isolated cases of swelling or redness around the implant site at day 62 (active) or 180 (placebo) are probably associated with tissue reactivity to the polymer and/or naltrexone. Both conditions resolved within 14 days without the use of additional medica-

tion. Overall, there was no obvious major tissue incompatibility observed at the implant site. This is consistent with human *in vitro* assessment indicating low-level tissue reactivity assessed by clinical examination, ultrasonography,⁹ and tissue biopsy specimen analysis.¹⁰ The overall low incidence of adverse events is also consistent with data on this implant from other researchers.²⁵

Although not classified as adverse events, 6 patients withdrew from the trial without evidence of returning to heroin use. A review of their clinical and research data regarding type and quantity of opioid use at baseline, severity and duration of withdrawal symptoms, and non-opioid drug use before or after study entry did not identify any variables that explained why more implant ($n=4$) than oral ($n=2$) naltrexone group participants withdrew. However, as shown in Figure 1, 3 implant group participants opted to receive another implant when they withdrew from the study.

One potential concern associated with effective naltrexone maintenance has been that previously heroin-dependent persons may shift from opioid to nonopioid drug use.³¹ Similar outcomes were found for the 2 groups, but the high prevalence of nonopioid drug use suggests that clinics providing opioid antagonist treatment should include procedures to identify and manage nonopioid drug use. In addition, naltrexone treatment may reduce tolerance to opioids or increase sensitivity, resulting in an increase in opioid overdoses when patients cease naltrexone treatment.³² Therefore, the absence of any opioid overdoses among those treated with oral or implant naltrexone is reassuring. We have received ethics approval to continue monitoring outcomes in this cohort to determine whether these results are maintained for 24 months.

Previous research has generally shown limited clinical efficacy in treating opioid dependence with daily oral naltrexone,³³ although the heterogeneity of interventions and outcome measures limits the conclusions that can be drawn.^{5,6} It has also been suggested that oral naltrexone is most effective for treating highly motivated patient groups, such as physicians or those being threatened with legal sanction.⁵ That more than 20% of oral naltrexone group participants were abstinent and a smaller percentage had not returned to regular heroin use by 6 months may reflect our inclusion of components known to improve outcomes with oral naltrexone, such as access to family therapy³⁴ or involvement of a non-drug-using, salient person, such as a family member or partner, to supervise and encourage daily use of oral medication.¹³

Study data indicate that this sustained-release implant is effective in retaining previously opioid (heroin)-dependent patients in treatment and that efficacy is improved compared with oral naltrexone. Therefore, sustained-release naltrexone implants appear to provide a new treatment option for patients with heroin dependence, particularly for those seeking an alternative to opioid agonist maintenance.

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