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Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial

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Background
Naltrexone has considerable potential in helping to prevent relapse in heroin dependency. A longer-lasting formulation for naltrexone treatment is desirable to further reduce non-adherence and relapse during treatment of opiate dependence.

Aims
To evaluate the safety and effectiveness of a 6-month naltrexone implant in reducing opioid use after in-patient treatment.

Method
A group of 56 abstinence-oriented patients who completed in-patient treatment for opioid dependence were randomly and openly assigned to receive either a 6-month naltrexone implant or their usual aftercare. Drug use and other outcomes were assessed at 6-month follow-up.

Results
Patients receiving naltrexone had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period (both $P<0.05$). Blood tests showed naltrexone levels above 1 ng/ml for the duration of 6 months. Two patients died, neither of whom had received an implant.

Conclusions
Naltrexone implant treatment safely and significantly reduces opioid use in a motivated population of patients.

Declaration of interest
None.

Despite decades of research confirming naltrexone's pharmacological efficacy in blocking the actions of heroin,[1] its clinical usefulness has proved limited.[2] Many people who are opiate-dependent are reluctant or refuse to take naltrexone;[3,4] many others begin but do not continue treatment.[5–7] Sustained-release opioid antagonist treatment removes the requirement for patients to take daily doses of the medication,[8] and one depot naltrexone formulation has been shown to reduce heroin use safely and effectively for the duration of its 4-week release period.[9,10] Despite these advances, longer-lasting products are desirable in order to minimise patients' opportunity for between-dosage withdrawal and relapse. Preliminary studies indicate that one type of implantable naltrexone provides about 6 months' opioid receptor blockade and has a satisfactory safety profile.[11–20] No randomised clinical trial of these implants has been done and the question of efficacy is still unanswered. This paper reports the findings of a randomised clinical trial of the safety and effectiveness of naltrexone implants in opioid-dependent patients who had completed in-patient treatment. We predicted that patients with a naltrexone implant would use fewer opioids and have fewer overdoses; also, that they would be less depressed, and would have better outcomes for work, education and criminal behaviour at follow-up compared with patients randomised to usual aftercare.

Method

This multicentre clinical trial used a randomised, open-label, trickle-inclusion study design. Sample size was determined to be sufficient with 30 patients in each group at a 5% significance level, assuming that the implant group would reduce their heroin use by 6 days relative to the control group in the month preceding follow-up. Patients were recruited from in-patient drug clinics in south-eastern Norway from 1 January 2006 to 1 July 2007, in a coordinated effort between two centres: the Norwegian Centre for Addiction Research at the University of Oslo and the Addiction Unit, Sørlandet Hospital, Kristiansand.

Study participants

Participants ($n=56$) were opiate-dependent adults (aged 18 years or above) receiving abstinence-oriented in-patient treatment. Staff members in the social and treatment services were asked to inform all opioid-dependent patients about the project and contact study staff for referral of volunteers. Patients who passed the initial assessment were contacted at the end of their detoxification or residential treatment stay for informed consent, baseline assessments of outcome instruments, and randomisation. Patients were allowed to talk freely about implantation and participation both prior to and after entering into the trial. Exclusion criteria were psychosis, pregnancy and serious hepatic disease. As liver transaminase levels decreased in a previous investigation of safety,[20] latent hepatitis C was considered not to represent a problem.

Randomisation

An independent statistician used a computer to generate a randomisation list for each of the two centres using a stratified permuted block protocol, assigning patients to one of two groups with block sizes of $n=100$ and $n=20$ for centre 1 and centre 2 respectively. An open-label (non-masked) randomisation procedure was used in the allocation of patients to groups, with envelopes containing allocation information sealed and numbered serially by staff independent of the study. Patients were informed of the project during their in-patient stay, and, if interested, enrolled shortly before regular discharge. The inclusion procedure comprised written informed consent and written product information. After the written informed consent was signed, and interview and questionnaires had been completed, the allocation

envelope was opened in the presence of the patient. All participants were informed that after the 6-month trial period those in the control group would be offered implantation and those in the implant group offered reimplantation. The study was approved by the regional ethics committee of southern Norway, and funded by a grant from the south-eastern Norway regional health authority. The trial registration number is NCT00521157.

Interventions

Naltrexone implant

Patients allocated to the implant group were given 20-pellet naltrexone implants (GoMedical Industries, Subiaco, Western Australia), previously found to block opioids for 5–6 months.[14,16,20] One doctor at each centre received a week of training in Perth, Western Australia, in 2005 to ensure that implantation procedures matched the manufacturer's standards and were conducted in a similar fashion at the two centres. All participants had to pass an oral naltrexone challenge (25 mg) before starting implant treatment. For the surgical procedure the skin of the lower abdomen was cleaned with chlorhexidine (0.5%). Local analgesic drugs were injected (10 ml 1% lidocaine, 20 ml 0.5% bupivacaine with adrenaline, 30 ml sodium chloride solution) and a 1.5 cm incision was made. Forceps were used bluntly to prepare a pocket in the subcutaneous tissue before inserting 20 pellets containing approximately 2.2 g naltrexone. The incision was closed using a non-absorbable polypropylene suture. A follow-up appointment was scheduled 7 days later for inspection of the wound and suture removal. Women participants were advised to use contraception during the study period. Implantation and participation were free to all participants. Implants were bought from the manufacturer at a discount. In case the participants given an implant required medical attention with analgesics during the study period, these patients were given an implant carrier's card which specified the presence of a naltrexone implant, its expected duration, possible options for providing pain relief and contact details for study staff. Blood samples for analysis of study medication were taken at stitch removal and after 6 months, and more frequently at staff's convenience for a small number of patients.

Usual care

Study staff encouraged all patients to contact relevant aftercare services before discharge from in-patient treatment, stressing the 50/50 chance of being randomised to the control group. Among the services available to these patients were out-patient counselling, application for entry to the Norwegian maintenance treatment programme,[21] readmission to detoxification or residential treatment, and vocational counselling and social services. If necessary, participants were assisted in locating and contacting the relevant treatment providers in their community.

Outcome measures

Primary dependent variables were self-reported opioid use (heroin, morphine, codeine, methadone or buprenorphine) and number of overdoses at 6-month follow-up. The Addiction Severity Index (ASI) is a structured interview covering drug use, physical and mental health, work, education, and criminal behaviour.[22] The main drug use outcome measures were the number of days of drug use in the 30 days preceding the interview, and a four-point frequency-of-use scale for the whole 6-month period (0, no use; 1, maximum two or three times per month; 2, two or three times per week; 3, daily or almost daily use). Timeline follow-back is an interview technique that uses backtracking and questioning about use and abstinence to obtain as accurate an estimate as possible of total number of days' use of a specific substance in the 180-day study period.[23]

Secondary dependent variables were: use of other drugs and alcohol; meeting criteria for opioid dependence and abuse diagnoses according to DSM–IV,[24] using the Mini International Neuropsychiatric Interview (MINI) version 5.0;[25] work status and criminal behaviour (Europ-ASI);[26] depression using the Beck Depression Inventory and the depression subscale of the 25-item Hopkins Symptom Checklist;[27,28] life satisfaction using the Temporal Satisfaction With Life Scale 'present' items;[29] and a visual analogue scale of condition satisfaction on a scale of 0–100 mm on the question, 'How satisfied/dissatisfied are you with having had/not having had an implant in the previous 6 months?' A similar scale was used for the question, 'How much/little would you recommend implants to a friend who was in a similar position to you when you joined this study?' with 0 indicating 'not at all' and 100 'very much'. A 0–100 scale was used for a question on craving-related thoughts: 'How much have you been bothered by thinking about opioids or their use in the past 6 months?' with 0 indicating 'not at all' and 100 'constantly'.

For patients living in a controlled environment (prison or clinic) at the time of follow-up, pre-admission data were taken to represent the remainder of the follow-up period. For patients estimated to be at risk of not completing the follow-up interview and/or questionnaires, priority was given to obtaining data on drug use (ASI and timeline).

Self-reported opioid use was verified against hair samples taken at the 6-month follow-up assessment. Despite the use of the more accurate liquid chromatography–tandem mass spectrometry (LC–MS–MS) method,[30] we still expected other methodological limitations to influence the accuracy of verification.[31] Examples of this could be participants without any hair, individual differences in hair growth rate, or inaccuracies in the sampling procedure making segmentation difficult. To adjust for these inaccuracies, concordance was calculated using a simplified procedure whereby occurrence of opioids or metabolites in hair (morphine, 6-monoacetylmorphine, codeine, methadone or buprenorphine) was matched to self-reported opioid intake for the study period as a whole. In this comparison, limit of quantification cut-off levels for the LC–MS–MS method were used.

In accordance with current regulatory requirements for clinical trials, unexpected adverse events related to the treatment under investigation were reported to relevant authorities. Less severe incidents were noted in the patient's file. Participants were collectively insured against damages resulting from receiving the treatment.

Statistical analysis

Analyses of efficacy were done on the intention-to-treat sample, with last response carried forward for any missing data. For missing responses that lacked an equivalent item at inclusion (i.e. satisfaction with group allocation), the worst recorded score in the group on the given item was copied. Separate analyses were done for a treatment completers group, which excluded patients who had died, were lost to follow-up or had had their implant removed. Group differences were analysed using a two-way analysis of variance (ANOVA) with Bonferroni correction. Centre, gender, any significant pre-treatment differences between groups and any treatment factors (e.g. urinalysis regimens, counselling) were controlled for. Variables were checked for violations of the normality assumption using Levene's test and residuals. Any variables found to violate the test were reanalysed using the rank transformation or non-parametric procedure. For dichotomous

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variables such as fulfilment of DSM–IV diagnostic criteria, the Cochran–Mantel–Haenszel test was used to calculate odds ratios, with Fisher's exact test used for tests of significance in small samples. The Statistical Package for the Social Sciences (SPSS version 16 for Mac) was used for all statistical analyses, except for numbers needed to treat (NNT), which were calculated using the online Randomised Controlled Trial NNT calculator from the Center for Evidence-Based Medicine at the University of Toronto.

Results

Age and gender demographic data for the study sample (Table 1; further details are given in online Table DS1) were similar to those of the total population of patients in the 15 clinics, where the mean age was 34 years and 33.5% were women. The CONSORT flowchart for inclusion and analysis of patients can be seen in Fig. 1. The main reasons for ineligibility were not completing treatment as planned, awaiting transfer to other clinics and starting maintenance treatment. After randomisation the two study groups did not differ significantly on any variable except for benzodiazepine use (Table 1), where the implant group had significantly more years of use in their lifetime than the control group. The implant group had non-significantly more weeks in a controlled environment before inclusion, averaging 27 weeks (s.d. = 34.2) *v.* 12.6 weeks (s.d. = 42) for controls ($P = 0.17$). Most patients in the sample were injecting drug users (Table 1), and 26 of 29 in the implant group and 25 of 27 in the control group used more than one drug. The last participant completed follow-up by January 2008, with mean follow-up times being 187 days (s.d. = 21) since implantation for the implant group and 181 days (s.d. = 24) since inclusion for the control group (difference: $P = 0.38$, 95% CI −18 to 7).

Fifty-two patients (93%) were followed up at 6 months. Two patients were lost to follow-up (but confirmed by treatment staff to be alive at 6 months) and two died, one in each group. The death in the implant group was one of three patients who discharged themselves from the clinic, thus avoiding implantation. Eight patients in Kristiansand failed or refused to complete forms, and for this reason it was not possible to control for the influence of centre as a factor on measures of depression and of life or treatment satisfaction.

Plasma levels of study medication

Plasma levels from the 14 patients who presented themselves for testing were of similar distribution to previous trials,[20] with levels of naltrexone staying above 1 ng/ml for the duration of 6 months and above 2 ng/ml for about 5 months. Levels of the metabolite 6-β-naltrexol had a similar distribution.

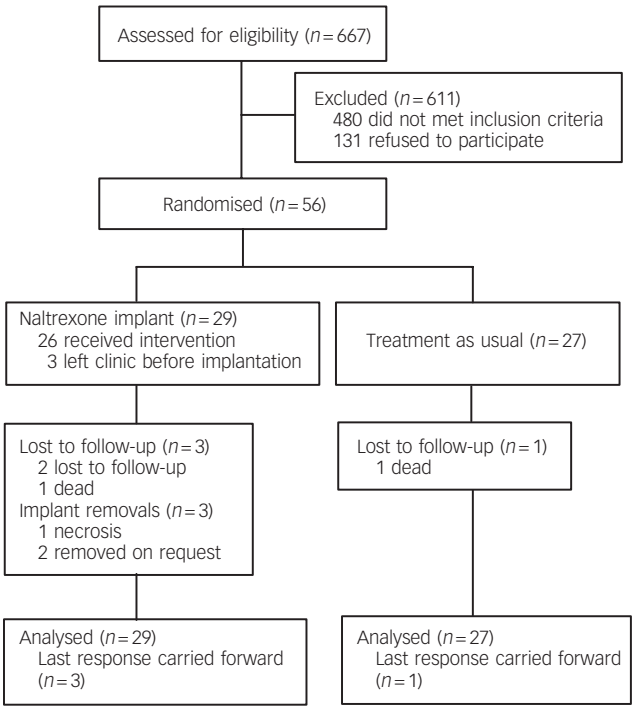

Fig. 1 CONSORT flowchart of patients screened, included, randomised, lost and analysed (omitting those not dependent on opioids).

Outcomes

Opioid use

Using intention-to-treat (ITT) analyses on the 56 included patients, the implant group reported use of significantly less opioids than controls on all opioid use outcome measures (Table 2). On the 180-day timeline follow-back, the implant group reported heroin use on an average of 17.9 days (s.d. = 41.8) and opioid use on 37 days (s.d. = 63.8), compared with 63.6 days (s.d. = 70.6) and 97.1 days (s.d. = 80.9) respectively for controls. These were reflected in significant differences in the ASI 30-day variable, with the implant group reporting a mean of 3.5 days (s.d. = 7.4) and 6.3 days (s.d. = 1.5) of heroin and opioid use

Table 1 Demographic characteristics of the sample

	Whole sample ($n = 56$)	Implant group ($n = 29$)	Control group ($n = 27$)	*P* value of difference
Female, *n* (%)	20 (36)	11 (38)	9 (33)	0.79
Age, years: mean (s.d.)	34.2 (8.6)	34.5 (8.0)	34 (9.4)	0.84
Substance use, years: mean (s.d.)				
Heroin	7 (5.3)	7 (5.0)	6.9 (5.6)	0.98
Morphine, codeine	2.2 (4.2)	2.8 (5.1)	1.6 (3.1)	0.30
Benzodiazepines	5.4 (6.4)	7.3 (7.2)	3.3 (4.8)	0.02*
Heavy alcohol use	3.3 (5.9)	3.9 (7.1)	2.8 (4.3)	0.56
Amphetamines	4.3 (5.2)	4.7 (4.9)	4 (5.6)	0.62
Polydrug use	9.5 (6.5)	10.7 (6.9)	8.2 (5.8)	0.14
Injecting drug users, *n* (%)	47 (84)	24 (83)	23 (85)	0.55
Overdose, lifetime number: mean (s.d.)	5 (7)	6 (8)	4 (6.6)	0.37

*$P < 0.05$.

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Table 2 Analysis of variance for primary outcome variables at 6-month follow-up

	Intention-to-treat sample ($n=56$)			Treatment completer sample[a] ($n=49$)		
	Mean difference	*F*	95% CI	Mean difference	*F*	95% CI
Heroin						
Timeline: days used in past 180 days	45.6*	7.0	14.1–77.3	57.8**	13.3	28.2–87.4
ASI: days used in past 30 days	8*	5.8	1.8–14	9*	6.9	2.8–15.3
All opioids[b]						
Timeline: days used in past 180 days	60.2**	8.1	20.9–99.5	73.5**	14.8	37.3–109.8
ASI: days used in past 30 days	9*	5.4	1.6–16.4	11.2**	9.2	4–18.5

ASI, Addiction Severity Index.
a. Patients who completed treatment and attended follow-up.
b. The 'all opioids' variables are sums of self-reported data on use of heroin, morphine, codeine, methadone and buprenorphine.
*$P<0.05$; **$P<0.01$.

respectively compared with the control group's 11.4 days (s.d. = 13.9) and 17.4 days (s.d. = 14.3). On the ASI frequency scale the implant group scored on average 0.8 (s.d. = 0.98) compared with 1.5 (s.d. = 1.3) in the control group, a difference of 0.73 ($P<0.05$, 95% CI 0.11–1.34); the mean score for use of all opioids on this scale was 0.92 (s.d. = 1.0) for the implant group and 2.0 (s.d. = 1.2) for the control group (difference: $P<0.001$, 95% CI 0.45–1.7. These ITT results include last observations carried forward for patients lost to follow-up and those who had implants removed.

Differences in self-reported opioid use increased when analyses were restricted to the 49 participants who completed treatment: 180-day timeline data for the implant group were 5.9 days (s.d. = 15) for heroin use and 20.4 (s.d. = 42.6) days for opioid use *v.* the control group's 63.7 days (s.d. = 72) and 93.9 days (s.d. = 80.8). In the 30 days prior to the follow-up assessment, those completing naltrexone treatment used heroin on an average of 2.85 days (s.d. = 7) and opioids on an average of 6.3 days (s.d. = 11.5) compared with the control group's 12 days (s.d. = 14) and 17.5 days (s.d. = 14.3) respectively. The ASI frequency results for those completing treatment were 0.6 (s.d. = 0.8) and 0.9 (s.d. = 1.0) for heroin and opioid use respectively, while heroin use frequency for completers in the control group was 1.5 (s.d. = 1.3) and 2 (s.d. = 1.2) for opioid use. Differences were significant at $P=0.003$ for heroin (mean difference 0.92, 95% CI 0.32–1.53) and $P<0.001$ for use of all opioids (mean difference 1.1, 95% CI 0.45–1.7). The number of patients abstinent from all opioids for the whole 180-day period was not significant in any of the analyses, with abstinence reported by 5 of 27 in the control group and 11 of 29 in the implant group in ITT analysis. Abstinence figures for the treatment completers sample were 5 of 26 and 11 of 23 for the control and implant groups respectively.

Overdoses

There was no significant difference between groups on self-reported overdoses (three in the implant group and four in the control group), nor was there any difference in the overdose mortality rate between groups. Two patients (one in each group) died of overdose. The death of the patient in the implant group occurred prior to naltrexone implantation, but was counted in the implant group in accordance with principles of ITT analysis.

Hair analysis concordance

Hair samples were available from 43 of 56 patients. Of the 13 patients who did not give hair, 2 were dead and 2 were lost to follow-up, whereas 4 in the implant group and 5 in the control group either had no hair or refused to have samples taken. The results of hair analysis matched self-reported opioid use in 37 of 43 available patients (86%). Urine samples were not taken, but might have provided a better measure of concordance.

Secondary outcomes

The naltrexone implant group scored lower than the control group on measures of polydrug use and craving-related thoughts, and higher on treatment satisfaction (Table 3). At the 6-month follow-up assessment, 18 of 27 controls *v.* 9 of 29 implant patients in the ITT group met criteria for DSM–IV opioid dependence using MINI (OR = 0.225, $P=0.015$, 95% CI 0.07–0.69). In the naltrexone completers group, only 3 of 23 patients qualified for this diagnosis, compared with the 17 (of 26) who met sufficient criteria in the control completers group (OR = 0.08, $P<0.001$). On this basis the NTT was 2.8 (95% CI 2–9) for the ITT analysis and 2.36 (95% CI 2–6) for the treatment completion sample. For the opioid abuse diagnosis using MINI, differences did not reach significance in the ITT sample, but were significantly in favour of

Table 3 Group differences on secondary outcome variables at 6-month follow-up

	Intention-to-treat sample ($n=56$)			Treatment completer sample[a] ($n=49$)		
	Mean difference	*F*	95% CI	Mean difference	*F*	95% CI
Polydrug use in past 30 days[b]	6.4*	4.2	0.6–12.3	6.5*	4.5	0.89–13.2
Craving[c]	27**	7.2	9.4–44.2	38.5**	18.9	21.6–55.5
Life satisfaction (TSWL score)[d]	5.4*	5.3	0.68–10.1	6*	6.5	1.2–10.7
Recommend implant to friend[c]	28.5*	9.1	10.8–46.2	22.5*	7.1	12.6–47.6
Satisfaction with treatment allocation[c]	42**	25	25.9–58.5	44.7**	11.6	24.8–58

TSWL, Temporal Satisfaction With Life.
a. Patients who completed treatment and attended follow-up.
b. Range 0–30
c. Range 0–100.
d. Range 5–35.
*$P<0.05$; **$P<0.01$.

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the naltrexone implant group in the completer sample (OR = 0.18, $P = 0.016$, 95% CI 0.48–0.68). The control group had significantly more detoxifications in the study period, with a mean of 0.71 detoxifications (s.d. = 0.98) *v.* 0.21 (s.d. = 0.41) for the implant patients in the ITT analysis (mean difference 0.53, $P = 0.010$, 95% CI 0.14–0.9). For the completers, sample means were 0.65 (s.d. = 0.9) for the control group and 0.13 (s.d. = 0.34) for the implant group (mean difference 0.52, $P = 0.011$, 95% CI 0.13–0.9).

Quality of life scores on the Temporal Satisfaction With Life Scale were higher for the implant group compared with controls (Table 3). Injection drug use in the 30 days preceding follow-up was lower among naltrexone patients (Mann–Whitney *U*-test, $Z = -2.1$, $P = 0.035$). There was no significant difference between groups on measures of depression, work, criminal activity, out-patient treatment attendance or the use of alcohol or non-opioid drugs.

Treatment satisfaction

The implant group rated their satisfaction with treatment highly, with a mean score in the ITT sample of 78 (s.d. = 22), and a reported likelihood that they would recommend naltrexone treatment to a friend of 85 (s.d. = 20). Scores were higher in the completer sample, with a mean satisfaction score of 87 (s.d. = 16) and a recommendation likelihood score of 91 (s.d. = 15) (Table 3).

Adverse events

One patient who had been allocated to the implant group left detoxification before implantation and died of an overdose after 4 days. One person in the control group died of an overdose 3 months into the study. Four non-fatal overdoses were reported among the control group. One patient in the implant group reported three overdoses while using combinations of opioids, amphetamines and benzodiazepines. Other complications associated with the intervention included the following: one patient had the naltrexone pellets removed owing to infection with necrosis at the implant site, and two others had the pellets removed at their own request after experiencing subjective discomfort (site pain for the first patient, diarrhoea for the second) for which they did not wish to await a full medical examination; two patients reported wound opening with leaking of fluid, which was treated with antibiotics without further complications; and three patients had allergic reactions that were successfully treated with antihistamines. Other adverse events were mild and in line with expectations from previous safety studies.[20] There was no recorded attempt at self-removal of capsules or any reported suicide attempt during the study period.

Discussion

Naltrexone implants were found to reduce opioid use in a sample of opiate-dependent patients motivated for this treatment. Improvements were found in key outcome areas including use of heroin, codeine, methadone and buprenorphine, as well as in polydrug use, injecting behaviour and quality of life. These changes represent important treatment gains and offer a valuable opportunity for behavioural, social and rehabilitative changes. Satisfaction with treatment was high, and adverse events were not more frequent or serious than in other treatments available for this group.

Limitations and strengths

A limitation of this study is its lack of masking. It is possible that psychological effects might have had an impact on the study findings. Open allocation was chosen as a result of previous experience of treating patients with implants,[20] which led us to anticipate that some people in this group would be likely to test the naltrexone blockade with opioids at least once during the 6-month study period. This would have compromised masking procedures, and might have left participants in a placebo group with an increased risk of overdose as a consequence of participation. Such concerns seem, to some extent, to have been justified: by the end of the study, more than half of patients with implants reported having tried opioids at least once. None the less, the lack of masking means that it is not known to what extent the results were influenced by psychological factors related to the intervention. A comparison with oral naltrexone was not done in this study.

Internal validity may have been affected by having too few inclusion criteria to secure a homogeneous patient sample and by not providing standardised aftercare instead of the uncontrolled usual care. However, statistical analyses of possible confounders showed most differences to favour the control group (e.g. years of benzodiazepine use), and there was no difference between the groups on aftercare variables. These factors would not, therefore, have altered the results to the advantage of the implant group. Although the use of existing treatment services in this study may mean the external validity of the findings is good, the sample is too small to make definite conclusions about generalisability.

Significance of follow-up implantations

Although there was a possibility of psychological influences on implant patients, there were also indications that participation influenced the abstinence rates among the control group. In at least three cases patients in the latter group stated that they had used the option of implantation at the end of the study as a cognitive strategy to avoid opioid use by counting days to implantation and telling themselves they would not be able to discontinue opioids again in time. Previous research has shown that having a coping strategy is indicative of non-relapsing patients.[32] This also suggests the strong motivation of some patients in obtaining this treatment. Offering implantation at follow-up may thus have contributed to the retention of participants in both groups, as all had entered the study with the intention of trying the treatment, and a majority of patients expressed interest in two implantation periods.

Role of motivation

Several aspects of the study point to the high degree of motivation among the participants. Previous research suggests only a minority of opioid-dependent patients in treatment are motivated to accept medication-induced opioid blockade.[4,6] Other indicators of the high level of motivation were the absence of self-removal attempts and the high retention rate. There were few other indicators that this sample was different from most other opioid users in these clinics at the time of recruitment. This may reflect that the distinguishing characteristic of this sample was not to be found in factors such as age, gender or years of drug use, but in differences of motivation for abstinence.

Rehabilitation

Self-reported overdose was not significantly influenced by naltrexone treatment in this study. However, the fact that none of the implanted patients died from overdose is consistent with the original hypothesis that naltrexone implants provide considerable overdose protection. Non-opioid drug use can also result in overdose, but without opioids present or exerting their effect,

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the risk of death is usually much reduced. This is the pattern that seems to best fit the data, as non-opioid drug use was common among the patients with implants who reported overdose. The three patients with implants who qualified for an opioid dependence diagnosis in MINI were individuals who had relapsed to previous polydrug-using ways, which included opioids, and their subjective reports satisfied the behavioural criteria needed for the diagnosis using this instrument. This study was not designed to verify whether actual opioid agonism was achieved. Despite the lack of progress in some areas, patients with implants expressed considerable satisfaction with the treatment, and the reduction in opioid use seems to have been sufficient to make a difference to their perceived quality of life. Improvements on outcomes not directly related to opioid use might require additional interventions. Treatment interventions targeted at non-opioid substance misuse might be able to take advantage of naltrexone's general craving-reducing effects.[33–35] Combined with the reductions in opioid use and these patients' high motivation towards abstinence, naltrexone implants look set to offer new opportunities to patients, clinicians and service providers.

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