ORIGINAL ARTICLE

A comparison of oral and implant naltrexone outcomes at 12 months

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ABSTRACT

Naltrexone's current use has been limited by compliance. Subcutaneous implants would seem to offer a solution to this problem and improve long-term outcomes. The aim of the present study was to compare groups of patients who had received oral naltrexone or a naltrexone implant after detoxification and to follow their progress. Forty-one patients received an implant, and 42 patients received oral naltrexone. They were surveyed at one, three, six, and 12 months after detoxification. Their designated support person was also contacted to confirm the self-reports of the participants. Patients were compared on gender, age, and length of time since detoxification. Implant patients showed much higher abstinence rates, while those in both groups who were abstinent showed greater compliance to naltrexone (time spent in treatment) and attended more counseling sessions. Although the participants were not randomly allocated to each treatment condition, the preliminary evidence indicates that implants can improve compliance rates and outcomes.

Key words: naltrexone, implant, social support, compliance, opiate addiction

INTRODUCTION

Naltrexone, a potent opiate antagonist, has been shown to have valuable properties for the treatment of addiction to opiates such as heroin and methadone. The most important property is its ability to completely block the effects of heroin,[1] making relapse to regular opiate use almost impossible while it is being taken. Research has shown that a dose of 50 to 100 mg of oral naltrexone provides effective protection against heroin for two to three days, and with chronic dosing, no accumulation of naltrexone or its metabolites has been observed.[2,3] Naltrexone is nontoxic[2-4] and produces no clinically important side effects.[2,4-6] The main factor restricting naltrexone's widespread use in opiate dependency treatment is rate of noncompliance.[7-11]

The ability to resist and ignore drug misuse cues is not easy. Indeed, 50 percent of clients who left a three-week inpatient opiate detoxification program had misused opiates within several days of doing so.[12] This early relapse undermines any chance of success, as it does not allow the user the chance to implement new opiate-free behaviors and thoughts. Naltrexone offers no immediate reinforcement after use and discontinuation produces no adverse effects, making it easier to stop using it. This is in contrast, however, to heroin and methadone, which offer strong immediate reinforcement after use and adverse effects and withdrawal if they are discontinued.[13] Noncompliance to naltrexone-based treatment is of particular concern because tolerance is reduced after a period of abstinence from opiate use and, as such, patients who relapse are at an increased risk of overdose and death.[14]

Poor outcomes in the treatment of opiate dependency using naltrexone relate to shortened time in treatment; conversely, longer time in treatment has been related to better long-term outcomes.[15,16] Moreover, with no aftercare counseling, compliance strategy, or social support in place, studies have shown predictably poor long-term outcomes.[9,17,18] When naltrexone is combined with an effective aftercare program and social support to enhance compliance, however, results have been promising.[19,20] This view has been supported empirically for other drug addiction treatment services.[21,22]

One approach to the issue of noncompliance in naltrexone treatment has been the development of subcutaneous naltrexone implants. The latest development with these implants enables a slow release into the body.[3,23] This frees the patient of the mental battle they face when trying to remain compliant with oral naltrexone use and the need to sustain a support-person relationship as part of a compliance strategy. Several studies have indicated the excellent bioavailability of naltrexone in subcutaneous form.[6,13]

In summary, clinical studies of patients recovering from opiate addiction indicate that patients who are retained in counseling and who continue to take naltrexone tend to have better long-term outcomes compared to those who spend less time in counseling and who take naltrexone for shorter periods of time. The issue of compliance has led to poor outcomes when support is lacking and there is little or no follow-up counseling, and these problems persist because of low retention among those using oral naltrexone. In the context of the present study, it was hypothesized that patients using naltrexone implants would have improved compliance rates, increased total time in treatment, and with aftercare counseling, improved long-term abstinence rates, as compared to those taking oral naltrexone.

METHODS

Participants

As part of the present follow-up study, 83 patients and their support people were interviewed, with approximately one-half of the patients receiving implants and the other one-half receiving oral naltrexone. All participants had completed the program over an eight-month period 12 to 20 months before data collection was completed in September 2004. As part of the practice of Addiction Treatment and Psychology Services' treatment program, all patients had undergone some counseling and were kept in regular contact via telephone. Their appointed support person was also contacted. Data collection involved a telephone survey of the patient and their support person for corroboration of the patient's self-report regarding their drug use and compliance to naltrexone.

Implant

Implants produced by Go Medical Industries Pty, Ltd. (Subiaco, Australia; International Patent Application Number: PCT/AU01/01107), in cooperation with the Department of Pharmacy at Curtin University (Bentley, Western Australia) were used. Each implant was designed to contain approximately 1.7 g naltrexone hydrochloride that had an in vitro release rate ranging from 0.2 to 0.8 percent of their residual mass per day.[24] The naltrexone was encapsulated in poly-DL-lactide—a polymer similar to that used in dissolvable surgical sutures and screws—microspheres compressed into pellets. Each implant consisted of 10 pellets. Subjects were given a single (10 pellets; 1.7 g naltrexone) or double (2 x 10 pellets; 3.4 g naltrexone) implant, which was surgically inserted into the subcutaneous tissues on the right or left side of the lower abdomen, in the fat tissue below the waistline. The length of time the implant was expected to release therapeutic doses of naltrexone was three months (approximately 100 days) for a single implant and up to five months (approximately 150 days) for a double implant.[3,23]

Procedure

Before detoxification, all patients underwent a psychosocial assessment to determine whether or not they were suitable for the program. Suitability was determined by the client's motivation to be opiate free, their level of social support, any serious psychiatric diagnoses of mental illness, and any medical issues that would make the detoxification process dangerous.

Part of the psychosocial assessment also entailed the completion of two psychometric tests, the Beck Depression Inventory-II (BDI-II) and the Symptom Checklist-90-Revised (SCL-90-R). The BDI-II is a short inventory designed to measure depression. As a general rule, a BDI-II score ranging from 0 to 13 is considered minimal, 14 to 19 is considered mild, 20 to 28 is considered moderate, and 29 to 63 is considered severe. The SCL-90-R is a broad, multidimensional measure of psychological distress. Only one of the scores on the SCL-90-R was included for comparison between the two groups—the Global Severity Index (GSI). The GSI is the best indicator of overall psychological distress, combining the breadth and intensity of symptoms that are experienced. As an operational rule, a GSI T-score of 63 or greater is considered to indicate a positive risk for an actual psychological disorder. All participants were asked to rate their self-esteem and the quality of their primary relationships on a 0 to 10 Likert scale before and after treatment.

All patients were told before detoxification about the costs and benefits of oral naltrexone and naltrexone implants. Each patient signed informed consent forms before detoxification and another consent form before insertion of the implant, in accordance with the Helsinki Declaration of 1975. One of the consent forms included permission to release the data collected for research purposes and other information relating to the nature and risks attached to the detoxification procedure and the use of naltrexone. No patient received an implant at the time of detoxification, but did so a number of days later. This was to ensure that consent was given while they were drug free and to rule out any possible complications that may have arisen after the implant was inserted. Use of the implant was authorized under the Special Access Scheme of the Therapeutic Goods Administration.

Analysis

The data were collected over a period of 20 months and were based on self-report. Researchers called the patients and their support people, often in the evening,

Table 1. Characteristics of patients before detoxification from opiates compared with oral and implant naltrexone groups

Characteristics	Naltrexone implant	Oral naltrexone
Total male patients (percent)	25 (61)	26 (62)
Total patients detoxed from methadone (percent)	8 (20)	5 (12)
Total patients detoxed from heroin (percent)	26 (63)	30 (71)
Total patients detoxed from heroin/methadone (percent)	5 (12)	6 (14.5)
Total patients detoxed from other opiates (percent)	2 (5)	1 (2.5)
Mean years using opiates (± SD)	7.2 (5.0)	9.6 (8.8)
Mean years of education	10.6	10.8
SCL-90-R GSI T-score (mean ± SD)	68.7 (16)	63.5 (10.3)
BDI-II score (mean ± SD)	22.2 (10.3)	17.9 (11.7)
Mean heroin use (g)	0.66	0.75
Mean methadone (mg)	60	53.5
Mean counseling sessions	8.5 (SD 2.7; 2 months duration)	6.4 (SD 2.5; 1.5 months duration)
Age range (yr)	20 to 40	22 to 48
Mean age (yr)	26.2	32.3

BDI-II, Beck Depression Inventory II; SCL-90-R GSI, Symptom Checklist-90-Revised Global Severity Index; SD, standard deviation.

to verify information. If an individual used opiates only a few times (i.e., once or twice) since their detoxification (e.g., to test if the naltrexone was working), this was not considered a relapse. Rather, a relapse was defined as occurring in those people with opiate use daily or on most days, sporadic opiate use (weeks or months of regular use followed by weeks or months of abstinence), and/or a few days of use followed by nonuse on a regular basis.

Data were compared for significant differences using two-tailed t-tests with an α level set at 0.05.

RESULTS

Table 1 presents the characteristics of patients in the two groups (naltrexone implant and oral naltrexone) in terms of several variables, including age, gender, BDI-II scores, SCL-90-R GSI T-scores, years of education, length of time using opiates, whether detoxification was from heroin or methadone, and the number of days since detoxification (at the time these statistics were compiled). T-tests were conducted to see whether the groups differed significantly on mean age, years using opiates, years of education, daily heroin and methadone dose, SCL-90-R GSI T-scores, BDI-II scores, and days since detoxification. The differences were found to be nonsignificant with an α level of 0.05 for all of these variables.

Table 2 compares the two groups in terms of the social factors of self-esteem and general relationship quality pre- and post-detoxification for those people who were successful in their attempt to cease opiate use. The statistics reported are the means for the two groups. T-tests were conducted to determine whether the changes (i.e., improvements) in self-esteem and relationships were statistically significant for both groups. Statistical analysis comparing ratings pre-detoxification and at six and 12 months post-detoxification were highly significant with an α level of 0.01, showing the psychosocial benefits of abstaining from opiate use. T-tests showed that the differences in scores on a scale from 0 to 10 for the two groups in relationships (approximately 2.3) and self-esteem (approximately 3.8) before their detoxification were nonsignificant ($p = 0.81$ and 0.86, respectively). However, at six months the differences in the groups after detoxification were significant for self-esteem with an α level

Table 2. Mean ratings on social factors before and after detoxification		
Social factors measured	**Naltrexone implant**	**Oral naltrexone**
Self-esteem rating predetoxification	3.9	3.8
Self-esteem rating postdetoxification (six mo)	7.9	9.1
Self-esteem rating postdetoxification (12 mo)	8.7	8.3
General relationship quality predetoxification	2.4	2.2
General relationship quality postdetoxification (six mo)	7.8	9
General relationship quality postdetoxification (12 mo)	8.1	8.8
All ratings are based on a scale where 0 = disastrous and 10 = excellent.		

of 0.05 ($p = 0.018$), while the relationship ratings approached significance ($p = 0.055$), with the oral naltrexone group tending to do better. The differences between the groups when ratings were compared in the period from six to 12 months post-detoxification and for scores at 12 months were all nonsignificant, indicating that improvements in self-esteem and relationships tended to be maintained and also evened out over time. Average scores on self-esteem and quality of relationships at 12 months were approximately 8.5 for both groups.

Table 3 shows the reports by the patients and their support people of the time compliant to naltrexone, which is equated with time spent in treatment. Those who had an implant and relapsed to opiate use tended to do so after they believed the implant(s) had ceased being effective—the difference in time compliant to naltrexone between the abstinent and relapse groups was statistically significant at six and 12 months. Those with implants who were abstinent at six and 12 months estimated the implant was effective for approximately six months, whereas those who relapsed on the implant estimated the effective time as approximately four months. These differences were statistically significant. For those on oral naltrexone who maintained abstinence, the time compliant to naltrexone averaged four months, whereas those who relapsed took naltrexone for only three to six weeks on average. The time spent using oral naltrexone for those who relapsed was highly significant compared to the other three groups.

Table 4 shows the number of counseling sessions each group attended on average. None of the differences were statistically significant although, as expected, those who relapsed or were noncontactable attended significantly fewer sessions (four, on average) than those who were known to be abstinent (nine to 12 sessions).

Table 5 represents the number of people in each group who relapsed to opiate use. Follow-up reports showed that 19 of the 42 individuals taking oral naltrexone (45 percent) relapsed to opiate use or were noncontactable at six months, whereas only eight out of 41 individuals (19 percent) were using opiates or were noncontactable after receiving an implant at six months. This advantage was maintained for the implant group at 12 months, with relapse rates of 17 percent and 38 percent for that group and the oral naltrexone group, respectively.

DISCUSSION

In this study, patients received naltrexone implants, generally four days after detoxification, or else agreed to take oral naltrexone for a period of at least six months. For this latter group, a support person was identified who agreed to supervise the daily taking of the medication. As can be seen from Table 1, both groups were comparable in terms of age, gender, and mean number of days since detoxification. Table 1 also shows that the mean BDI-II scores were in the moderate depression range for the naltrexone implant group, and the moderate-severe depression range for the oral naltrexone group. There was a large amount of variance in depression scores, however, as indicated by the standard deviations for both groups.

One significant difference between groups related to gender and was common to both of them: women scored much higher in terms of depression (mean score 32, severe) compared to men (mean score 23, moderate). The mean SCL-90-R GSI T-scores were above the critical score of 63 for both groups (and for men and women), indicating that a large number of clients in both groups should be considered positive for diagnosis of a mental disorder.

Table 3. Group comparison of mean time using naltrexone		
Classification	**Naltrexone implant, mean days (SD)**	**Oral naltrexone, mean days (SD)**
Abstinent six mo	176.6 (68.1)	120.00 (104.8)
Abstinent 12 mo	187.3 (69.1)	123.21 (105.5)
Relapsed six mo	112.5 (50)	19.7 (31.7)
Relapsed 12 mo	120 (45.6)	30.1 (54.25)
SD, standard deviation.		

Both groups rated their self-esteem and general relationship quality comparably low before detoxification from opiates. As was hypothesized, both groups showed sharp increases in these ratings after detoxification; however, data were obtained only for those who were successful at abstaining from opiate use. It is interesting to note that the oral naltrexone group actually showed greater improvements on self-esteem and relationship ratings six months after detoxification; this may indicate a greater resolve within this group to "stay clean" and also closer reliance on their support people.

Compliance with naltrexone use was the main point of interest of this study (Table 3). It proved difficult to obtain precise information for those in the implant group who were abstinent, however, as the duration for which the implant was considered effective was based on their expectations about coverage and did not necessarily relate to the actual release of naltrexone. Information gathered from those who relapsed and who had the implant during the time of effective coverage was somewhat more accurate, as some patients tried using opiates for a period before they became aware that they could "feel it" and could therefore pinpoint the date it was no longer effective. Obviously the time spent using oral naltrexone was much more accurate to determine, as patients and support people were both clearly aware of when a patient stopped taking the tablets, although in many cases they had done so well before they relapsed. The expectation of those having a double implant was that it would be effective for up to six months. Estimates for this group were therefore higher than for those with a single implant, although in both groups many felt the implants were effective for longer than the actual duration patients were told the implants had.

A comparison of those in the oral group who maintained abstinence and those who relapsed show very clear differences in time spent taking naltrexone. At 12 months, those who were abstinent had taken naltrexone for an average of four months, whereas many of those who relapsed had ceased taking naltrexone within days of detoxification and the relapse group, on average, took naltrexone for only one month. Inspection of the results show that of those in the oral group who were abstinent at six months, only four (19 percent) stopped taking naltrexone less than one week after detoxification, and two (11 percent) had done so at 12 months. On the other hand, of those in the oral group who relapsed, 14 out of 21 (67 percent) had ceased taking naltrexone within a fortnight of detoxification, whereas at 12 months, 17 of 24 (70 percent) had stopped within two weeks.

The other result of note was that many still relapsed in the implant group despite being compliant to naltrexone for a similar period to those who were abstinent in the oral group. It seems there was a group who relapsed shortly after they believed the implant had stopped working and who possibly would have relapsed even sooner had they been on oral naltrexone. For both groups, it may be that some participants were not ready or were not suitable candidates for detoxification, and relapse was more likely among these individuals. It seems that if some of these potential relapsers are able to stay in treatment long enough, however, then better results are achievable given the overall better outcomes in the implant group.

The data in Table 4 show that participants who remained abstinent attended significantly more counseling sessions than those who relapsed and, while those who attended longer reported feeling better, it was also the case that if they relapsed they tended to drop out of treatment. However, because there was a cost to receive counseling, it may be that those who opted for oral naltrexone for financial reasons were also not able to afford counseling, thus compromising their outcomes.

The most important data to come from this study appear in Table 5, showing the clear advantage of a naltrexone implant over oral naltrexone. The difference between the two groups was quite striking, particularly when compared to traditional detoxification and rehabilitation programs.[15,16]

Table 4. Group comparison of mean number of counseling sessions attended		
Classification	**Naltrexone implant**	**Oral naltrexone**
Abstinent	12.7	9.0
Relapsed	4.0	4.9
Noncontactable	4.0	3.2
Total	8.5	6.4

Closer analysis of the relapse groups showed that those in the implant group who relapsed to heroin in particular had sold the drug before detoxification and continued selling afterward, had experienced early sexual or physical abuse and reported being able to get "over the top" of the naltrexone if they used enough, or else agreed that it didn't do anything, but used it anyway. They also reported that although they thought the heroin had only a weak effect, they still felt compelled to use, even while the implant was actively antagonizing the effect of the drug. This motivation contrasts with that found in the oral naltrexone group, as the participants knew they need only avoid taking the naltrexone tablets to receive the strong reward component associated with heroin use.

A large number in each group admitted to using heroin once or twice; however, the majority soon realized that it had no subjective effect, and knowing that it would only be a waste of time and money, went on to achieve abstinence during the study period. If any insight can be derived from this study, it is that those who were criminally inclined with a history of early delinquency and ongoing criminal behavior, irrespective of the need to obtain their drug (mainly men), and those who experienced abuse early in life and were inclined to use opiates to self-medicate (mainly women), seemed more likely to relapse. Notwithstanding, time spent in treatment had the effect of improving outcomes in general.

The other prominent feature of this study was the large number of people who were noncontactable, especially in the period from six to 12 months, during which this figure represented almost one-fourth of the participants in each group. These individuals may have been abstinent, but this could not be confirmed.

The present study would seem to provide strong preliminary evidence that the use of naltrexone implants is an effective solution to the problem of compliance, and that the effect tends to last for some time after the antagonistic effects of the implant have worn off. It seems that the lack of positive reinforcement (i.e., no subjective effect), strong negative reinforcement (i.e., wasting money) associated with using opiates, and lack of craving while an implant is releasing naltrexone into the body, are sufficient to prevent drug use. This allows time for the development of more adaptive coping behaviors, and for the patient, time to deal with the underlying psychological issues that so often compel people to use these drugs. It remains to be seen how many patients remain abstinent at longer follow-up intervals, although the trend seems to be that with more time spent in treatment and the ability to effect change in lifestyle, the more chance that long-term recovery will be sustained.

Overall, this study demonstrates the potential for naltrexone implants to improve compliance rates, increase time spent in treatment, and improve abstinence rates, as opposed to oral naltrexone.

Study limitations

This study would have produced more robust results if subjects had been randomly allocated to each treatment condition, whereas here patient groups were self-selected. Perhaps the patients who chose oral naltrexone might have been less motivated, selecting a treatment method that they felt they could opt out of at any point. Alternatively, this group may have felt they wanted to take responsibility for their own recovery and not proceed with the "easy way" of an implant, or as mentioned previously, it may have simply been that they could not afford the implant.

It is interesting to note that at the time of collecting these data, the ratio of people opting to use oral naltrexone compared to the implant has changed dramatically. Very few patients, who now come to our clinic for treatment, choose oral naltrexone (less than 10 percent), and many come to have an implant inserted after completing detoxification elsewhere. Reasons for not having an implant in the group we studied may have reflected some misgivings about the relative effectiveness of the implant or misunderstandings about how it worked, rather than financial concerns, as we assumed at the time. It seems that as word about the effectiveness of the implant has spread, financial concerns have not had as much influence.

This study also was comprised of patients who were screened for serious psychiatric problems, levels of motivation, and social support. Motivation was defined as the demonstration by intrinsic signs, and not by extrinsic signs, of behavioral hurdles placed in the path of a person who is already low on self-esteem and self-efficacy. As can be seen from our results, most patients were

Table 5. Group comparison for number of patients relapsed to opiate use		
Classification	**Naltrexone implant**	**Oral naltrexone**
Abstinent six mos	33 (80.5)	23 (54.5)
Relapsed six mos	6 (15)	15 (35.5)
Noncontactable six mos	2 (5)	4 (10)
Abstinent 12 mos	25 (61)	17 (40.5)
Relapsed 12 mos	7 (17)	16 (38)
Noncontactable 12 mos	9 (22)	9 (22)
Numbers in parentheses are percentages.		

moderately to highly depressed, and therefore tended to lack motivation. It has always been our contention that the use of naltrexone should be limited to those who have a reasonable chance of long-term recovery. That notwithstanding, it can also be seen that the patient group presented with a range of psychological problems that must be attended to, a history of multiple detoxification attempts, and often polydrug use. None of these problems was considered a bar to inclusion in the program. As other researchers have pointed out, naltrexone should be targeted to those who can most benefit, and the aim of research is to clearly define the best way to use this medication.[24]

In the present study, we relied on self-report and corroboration of support people to verify patient compliance to naltrexone and abstinence from opiates. Having patients give regular urine drug screens would also have lent more certainty to our reported results, especially effective levels of naltrexone.

Future research

Future research should include random allocation of subjects to each treatment condition, although matching on significant confounding variables may be warranted before random allocation. It is also important to maintain other strategies that have been shown to enhance outcomes and maintain the safety of the patients. Neither group maintained counseling for as long as it was felt desirable, and this often related to patient financial concerns. Not only is this in keeping with the research, but there is also a strong ethical argument to proceed in this manner and to ensure equal access to supportive counseling. Even with the provision of counseling, however, there appears to be a group of patients who are not likely to benefit from use of naltrexone and for whom methadone or buprenorphine is the preferred treatment.

To obtain valid data, it is important that future research also includes biological tests of opiate and other drug use to verify self-reports. Although regular checks of naltrexone levels and screening for opiates would lend more credence to the results, we are confident about the accuracy of the data collected. The timeframe for collection of data should also be extended to a point some years beyond the end of implant effectiveness. It is believed that the longer a person is in treatment the better the outcome, and certainly the use of implants facilitates this. However, it has yet to be shown that the use of naltrexone implants translates directly into long-term improvement.

The present study indicates the potential of the use of these devices in the treatment of opiate dependency. Clinical trials that are properly constituted with ethical approval and that extend well beyond the blocking effect of the implant, combined with biological testing of drug use, are necessary to confirm the results of this study.

ACKNOWLEDGMENTS

Funding for the detoxification process and naltrexone medication was supplied by the patients themselves, their families, and support people. Other costs associated with the study, including wages, telephone calls, consumables, and overheads to collect, collate, and analyze the data and write the paper were incurred by Addiction Treatment and Psychology Services. No one involved in the study had or has any commercial or other relationship with Go Medical Industries, the maker of the implant, any of its subsidiaries or associated companies, or personnel other than as a purchaser of the implants. The authors would also like to acknowledge the vital contributions of Therapy Director Mrs. Dawn Colquhoun. She has been involved not only with the development of the program, but also patient psychotherapy and training and supervision of other therapists. The study results could not have been achieved without her expertise and compassion.

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