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**Are Naltrexone Implants More Effective Than Oral Drug And/Or Behavioral Therapy At Reducing Heroin Use In Recovering Heroin Dependent Adults?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

**OBJECTIVE:** The objective of this selective evidence based medicine review is to determine whether or not a naltrexone implant is more effective than oral drug therapy and/or behavioral therapy at reducing heroin use in recovering heroin dependent adults.

**STUDY DESIGN:** Review of three English language primary studies published from 2007 to 2010.

**DATA SOURCE:** Three randomized controlled trails comparing naltrexone implants to oral naltrexone, methadone, and usual aftercare found using Ovid, Pub med and Cochrane databases

**OUTCOME MEASURED:** The primary outcomes measured by all three studies all three articles measured frequency of heroin use by self report

**RESULTS:** Hulse et al. found that significantly more patients were abstaining from heroin at the 6 month mark with implant naltrexone as compared to oral naltrexone. Kunøe et al. found that implant naltrexone was significantly better than usual aftercare at reducing total number of days of heroin use. Lobmair et al. found naltrexone implants to be similar to methadone treatment at reducing the number of days of heroin use per month.

**CONCLUSIONS:** Hulse et al. found implantable naltrexone is more effective than oral, and Kunøe et al. found it to be more effective than usual aftercare. Lobamier et al. concludes that methadone is equally effective to the naltrexone implant. These articles suggest that naltrexone implants are as or more effective than other therapies currently being offered. Future studies should be done in order identify individual patient factors that lead to higher efficacy and lower adverse events with implant therapy.

**KEY WORDS:** Naltrexone implant, Relapse, opioids, and heroin

## INTRODUCTION

Heroin dependence can be more broadly defined as opioid dependence, and is described in the DSM IV.<sup>1</sup> It is a disease that is extremely prone to relapse, and is commonly treated with oral naltrexone. Naltrexone is an opioid receptor antagonist which functions in blocking the effects of opioids. Although it is very effective when taken as directed, success is limited by the heavy reliance placed on recovering individuals to consistently self-administer daily doses of naltrexone. An implantable version of the drug has recently been devised as way of side-stepping this obstacle. The implant ensures that patients will have therapeutic blood levels of naltrexone for up to 6 months at a time, theoretically increasing efficacy.<sup>1-3</sup> One study even reports that while oral naltrexone has only been as effective as placebo in reducing heroin cravings, the implantable version shows a significant reduction in cravings.<sup>4</sup> This paper evaluates three randomized controlled trials that compare the effectiveness of the naltrexone implant to more traditional oral and behavioral drug therapies in reducing heroin use in recovering opioid dependent adults.

As a health care provider, it is important to be able to identify heroin dependent patients and provide them with the best resources currently available. This is especially relevant in the northeastern United States where heroin abuse is disproportionately high when compared with the rest of the country.<sup>5</sup> Data shows that individuals who begin abusing prescription opiates are at risk of later becoming heroin users in order to attain opiates more easily, at a lower cost, and achieve a greater “rush”. The rising prescription opiate abuse may be leading to higher rates of heroin abuse throughout the U.S. In fact, the number of users have risen substantially from 2002 to 2010.<sup>6</sup> Currently, these users are mainly concentrated in the Northeastern United states due to drug availability.<sup>5</sup> This trend can also be evidenced by the significant drop in age of first time

heroin use from an average of 25.5 years in 2009 to 21.3 years in 2010.<sup>6</sup> Due to the fact that opioid dependence is a chronic condition, it is likely that younger first time heroin users will lead to an increased population of heroin dependent adults in the future.

Increased numbers of dependent individuals will increase the cost of healthcare in this area. In 2010 approximately 417,000 individuals sought treatment for heroin dependence.<sup>6</sup> The Office of National Drug Control Policy estimates that by 2020 there will be about 27 million patients in need of treatment for various substance use disorders, and they are expressing a great need for more healthcare professionals to be trained in substance abuse treatment.<sup>7</sup>

Although current figures specific to the healthcare cost of heroin dependence are somewhat elusive, a 2001 study estimated the 1996 U.S. health care cost of heroin addiction to be over 5 billion dollars.<sup>8</sup> With the number of users increasing combined with rising healthcare costs, today's figures are likely to be substantially higher. Furthermore, the full economic burden of heroin addiction is great, easily more than four times the healthcare cost alone.<sup>8</sup>

Heroin puts a user at risk of an array health problems that come not only from its nature as an opioid, but from other factors as well. Many of these health risks are infectious, and come about as a result of frequent intravenous administration of the drug with contaminated needles and non-sterile injection sites. Hepatitis C, HIV, and bacterial infections of the injection site, blood, or heart valves are just a few examples. Some hazards come about as a result of the unregulated nature of heroin. Varying potencies between batches make dosing inexact and contribute to overdose, possibly leading to respiratory depression, coma, and death. A variety of additives may be found in impure heroin, many of which can cause vascular damage. Other health problems arise over time, mainly as a result of the patient neglecting his or her own health while spending more time and energy in pursuit of the drug.<sup>9</sup>

Numerous relapses usually occur before a patient is finally able to end his or her heroin use. This fact is particularly troubling when considering that patients are more susceptible to heroin overdose during periods of relapse.<sup>2</sup> In an attempt to minimize instances of relapse, opioid dependence is usually treated with a combination of behavioral therapy and medication. Medication used in treatment typically includes methadone, buprenorphine, or naltrexone.<sup>9</sup> Treatment length varies widely according to medication and individual patient progress. Patients are generally encouraged to attend support groups such as Narcotics Anonymous indefinitely.

Naltrexone is generally very effective when taken as directed, but poor medication compliance leads to mixed clinical efficacy. Although medication compliance is an issue with almost any patient population, it is of special concern when dealing with recovering heroin dependent adults. In early recovery, this patient population generally lacks the financial, social, and mental stability needed to reliably self-administer medication, and unfortunately, the price of relapse is extremely high. An implantable form of naltrexone would theoretically eliminate this issue by removing the need for daily medication compliance.<sup>1,2</sup>

## OBJECTIVE

The objective of this systematic review is to determine whether or not a naltrexone implant is more effective than oral drug therapy and/or behavioral therapy at reducing heroin use in recovering heroin dependent adults.

## METHODS

The three studies included in the systematic review were randomized controlled trials (RCTs). Hulse et al. was a randomized, double-blind, double-placebo controlled study.<sup>1</sup> Kunøe et al. used a randomized, open-label, trickle-inclusion study design.<sup>2</sup> Lobmaier et al. used a randomized, 2-arm, open-label study design.<sup>3</sup> The population that was studied included

recovering heroin dependent adults (18 years and older). The intervention being studied was a naltrexone implant designed release therapeutic naltrexone levels continuously for 5-6 months. These patients were compared against the control groups consisting of oral drug and/or behavior therapy. Oral drugs in the control groups included methadone in Lobmaier et al. and naltrexone in Hulse et al.<sup>1,3</sup> The outcome measured was heroin use. Hulse et al. reported heroin use dichotomously as either use or abstinence, Kunøe et al. reported it as total number of days using heroin over the 180 day study period, and Lobmaier et al reported the average number of days used per month.<sup>1-3</sup>

The Cochrane Database was searched first, followed by OVID and Pub med. Relevant articles published between December 2007 and September 2011 were included. Key words searched were Naltrexone implant, Relapse, opioids, and heroin. All articles were published in english in peer reviewed journals. Articles were selected based on their relevance and the importance of their outcomes to patients (POEMS). Studies included were randomized controlled trials, they measured outcomes important to the patient (POEMS), and included patients that completed detox and were beginning recovery from heroin. Any studies involving subjects under 18 years of age, or published in or before November 2007 were excluded. Statistics reported or used include p values, ANOVA F score, RRR, ARR, NNT.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Hulse <sup>1</sup> 2009	RCT	70	18 yrs or older	DSM-IV opioid (heroin) dependence, willing to be randomized, residing in the Perth, Western Australia, metropolitan area; completion of preclinical screening and written consent	3 + opioid overdoses in past month; treatment with oral naltrexone more than 4 times in the previous 3 months; previous sustained-release naltrexone treatment; enrollment in other opioid research; pregnancy; active skin or other infections; contraindications to naltrexone	9	Experimental group: single dose of 2.3 g of naltrexone implant (plus placebo tablets)  Control group: oral naltrexone, 50 mg/d, for 6 months (plus placebo implants)
Kunøe <sup>2</sup> 2009	RCT	56	18 yrs or older	Opiate-dependent adults receiving abstinence-oriented in-patient treatment	Psychosis, pregnancy, and serious hepatic disease	4	Experimental group: 20-pellet naltrexone implants (effective for 5-6 months)  Control group: Usual aftercare
Lobmaier <sup>3</sup> 2010	RCT	44	18 yrs or older	Heroin-dependent inmate, pre-incarceration heroin dependence, minimum of 2 months of sentence time remaining	Untreated major depression or psychosis, severe hepatic impairment, pregnancy, currently in an agonist maintenance treatment program	17	Experimental group: 20-pellet naltrexone implants (effective for 5-6 months)  Control group: Methadone treatment starting at 30 mg per day and increasing to the recommended daily dose of 80-130 mg within 3 weeks

## OUTCOMES MEASURED

All three articles measured frequency of heroin use by self report.

## RESULTS



Efficacy of the naltrexone implant for reducing heroin use compared to oral therapy and/or behavioral therapy was reported as dichotomous data in Hulse et al. and continuous data in Kunøe et al. and Lobmaier et al. All three studies performed intention to treat analysis. All three studies used the same intervention in their experimental groups (5-6 month naltrexone implant), and all three collected patient data over a 6 month period.<sup>1-3</sup> However, the intervention offered to each control group, as well as the way the data were reported varied between studies.

Hulse et al. offered oral naltrexone to the control group. They reported that only 7 out of the 34 patients were abstaining from heroin use in the oral naltrexone group at the end of six months, and 17 out of 35 were abstaining in the naltrexone implant group. This indicates that significantly more patients were abstaining from heroin at the 6 month mark with implant naltrexone as compared to oral naltrexone with a narrow 95% confidence interval (CI) of 0.90 - 3.28 (Table 2). The relative risk reduction (RRR) and the absolute risk reduction (ARR) were large, 133% and 28% respectively. The number needed to treat (NNT) was calculated to be 4, implying that one more patient would be abstinent at the 6 month mark for every 4 patients treated with implant instead of oral naltrexone (Table 3).<sup>1</sup>

Kunøe et al. only specified that the control group would receive some form of “usual aftercare” as their treatment. Usual aftercare involved behavioral and/or oral drug therapy, but varied from patient to patient. They reported that the control group of “usual aftercare” patients had an average of 63.3 days of heroin use over the 180 day study period. Patients in the naltrexone implant group had an average of 17.9 days of heroin use over that same time period. This was found to be significant, indicating that implant naltrexone may be better than usual aftercare at reducing total number of days of heroin use. The values are reported as  $p < 0.05$  and a

95% CI of 14.1 - 77.3 (Table 2). They also reported an ANOVA F-score = 7.0 and a change in mean from baseline of 45.6 days, both of which are significant.<sup>2</sup>

Lobmaier et al. offered methadone treatment to the control group. They found the mean number of days of heroin use per month to be 20.2 in the control group and 15.6 in the experimental group. This was not found to be significant ( $p > 0.05$ ). Large standard deviations (SD) in the number of days per month of heroin use in the control and experimental groups, 12.56 and 14.97 respectively, were reported (Table 2). The author, however, reports significantly less heroin use in the experimental group if worst case analysis is not applied ( $p = 0.012$ ).<sup>3</sup>

Table 2 - Efficacy of naltrexone implant at preventing heroin use in recovering adults

Study	Incidence of heroin use in control group	Incidence of heroin use in experimental group	p-value	Odds Ratio (95% CI)
Hulse <sup>1</sup> 2009	7/34 participants abstaining	17/35 participants abstaining	N/A	(0.90 - 3.28)
Kunøe <sup>2</sup> 2009	63.6/180 days	17.9/180 days	$p < 0.05$	(14.1-77.3)
Lobmaier <sup>3</sup> 2010	20.2 days per month	15.6 days per month	$p > 0.05$	N/A

Table 3 - Treatment effects

Study	RRR	ARR	NNT
Hulse <sup>1</sup> 2009	133%	28%	4

Hulse et al. reported several study related adverse events. In this study, the experimental group and control group received implants that were completely identical with one exception: placebo pellets were used in the control group's implants. Because of this, adverse events that related to the implantation site itself (wound swelling/erythema and wound hematoma) were calculated with the data gathered from all 69 participants. Furthermore, the data was calculated

with the assumption that use of oral naltrexone alone would not cause adverse events related to an implantation site. Under these assumptions, the number needed to harm (NNH) for the most serious adverse event, a wound hematoma, was 100. This suggests one wound hematoma will occur for every 100 patients receiving naltrexone implants. The NNH for implantation site erythema/edema was 34, making this less serious adverse event more likely. Other adverse events that were reported related to side effects of naltrexone itself. These adverse events include: erectile dysfunction, abdominal cramps, diarrhea, depression, metallic taste, and headache. With the exception of one patient who reported cramping and diarrhea at several of the follow-ups throughout the study, these medication side effects were only reported one time for each of the patients who experienced them. Considering the control and experimental groups had 34 and 35 members, respectively, Table 4 may not be representative of a larger population. However, diarrhea was found in 4 members of the experimental group (one member with persistent diarrhea) and none from the control group. This may be because the experimental group had blood naltrexone levels at or above therapeutic level significantly more frequently than the control group, and diarrhea is one of the most common known side effects of naltrexone (Table 4).<sup>1</sup>

Table 4 - Adverse events with implant vs oral naltrexone

Adverse Events	Oral CER	Implant EER	RRI	ARI	NNH
Wound Edema and Erythema	0% <sup>a</sup>	3% <sup>b</sup>	N/A	3%	34
Wound Hematoma	0% <sup>a</sup>	1% <sup>b</sup>	N/A	1%	100
Diarrhea	0%	9%	N/A	9%	12
Abdominal Cramps	0%	3%	N/A	3%	34
Erectile Dysfunction	0%	3%	N/A	3%	34
Headache	3%	3%	0%	0%	N/A
Depression	3%	0%	-100%	-3%	-34
Metallic Taste	3%	0%	-100%	-3%	-34

RRI= relative risk reduction; ARI= absolute risk reduction; NNH= number needed to harm; CER= control event rate; EER= experimental event rate

Negative NNH indicates benefit.
<sup>a</sup> Calculated assuming patients taking oral naltrexone without placebo implant would not develop implant-related adverse effects.
<sup>b</sup> Calculated assuming placebo and naltrexone implants would have similar implant-related adverse effects.

Lobmaier et al. reported compliance rates of study treatment in former inmates. In this study, the population focused on inmates with heroin dependence who were soon to be released from prison. In each case, detoxification began about a month before each inmate was released, and data was collected up to 6 months after release. Six months after beginning treatment, 69.6% of patients in the naltrexone implant group were continuing to receive the study-assigned treatment while only 23.8% of inmates in the methadone control group were receiving treatment. This indicates a significantly higher compliance rate ( $p=0.003$ ) for inmates with naltrexone implants vs. oral methadone.<sup>3</sup>

## DISCUSSION

Although the articles discussed in this paper focused on adults who were recovering from heroin dependence, naltrexone is effective in treating dependence of other opiates as well as alcohol. Consistent daily compliance with oral medication is an area of concern when treating any of these patients, and some studies are looking into the efficacy of the naltrexone implant in these populations.<sup>1</sup>

Although the active component of the naltrexone implant has been FDA approved and widely used in the treatment of opioid dependence since 1984, the implantable version of the drug has not yet gained FDA approval in the United States.<sup>1</sup> Despite this, some private U.S. clinics have been using the implant. These implants are in the form of naltrexone containing pellets formed with a biodegradable polymer. They are surgically implanted into a patient's

abdominal wall. Sustained release naltrexone is currently approved in an injectable form under the trade name Vivitrol, however, this must be given on a monthly basis.<sup>1, 2, 10</sup>

Naltrexone has been reported to cause nausea/vomiting/diarrhea, abdominal pain/cramping, constipation, depressed mood, difficulty falling/staying asleep, drowsiness, headache, anxiety/nervousness, irritability, rash, and muscle/joint pain. Among these, GI effects are the most common, and may occur in up to 10% of patients. More rare but serious side effects include confusion, severe vomiting/diarrhea, and hallucinations.<sup>10</sup>

Naltrexone is contraindicated in patients with hepatic failure or acute hepatitis, patients taking opiate agonists, patients who have a current physical dependence to opioids, and patients with hypersensitivity to naltrexone or other ingredients in the given formulation. Patients should be opiate free for 7-10 days before beginning naltrexone therapy, as it can cause acute withdrawal. Naltrexone is relatively contraindicated in patients with active liver disease (LFTs 3 times the upper limit of normal). Because naltrexone metabolites are eliminated in urine, it should be used with caution in patients with moderate to severe renal impairment. The implantable version of naltrexone has some additional contraindications. These include infection of the implantation site and bleeding disorders.<sup>10</sup>

The search for this systematic review was limited to articles published after November 2007. The articles themselves also had some limitations. The lack of blinding in Kunøe et al. and Lobamier et al. was one of the most important.<sup>2, 3</sup> Also, the diversity of treatment regimens of the control group from Lobermier et al. limits the studies ability to make a straight forward comparison between treatment modalities.<sup>3</sup> Finally, the sample sizes in all three studies were small, limiting the generalizability of the findings.

CONCLUSION

The evidence as to whether or not a naltrexone implant has better efficacy than oral therapy is conflicting. Hulse et al. supports the idea that implantable naltrexone is more effective than oral.<sup>1</sup> Kunøe et al. also found the implant to be more effective, however, the control group here lacked the uniformity needed for a clear comparison.<sup>2</sup> Lobamier et al. concludes that a different oral therapy, methadone, is equally effective to that of the naltrexone implant.<sup>3</sup> It is important to note, however, that methadone itself is an opiate. This type of treatment is principally very different from treatment with the opiate antagonist naltrexone. Given the above information, it seems that naltrexone implants would be a viable option for recovering heroin dependent adults. They would be especially useful in patients with opioid dependence who have found oral naltrexone to be effective at reducing cravings in the past, but failed therapy due to poor medication compliance.

It is seldom the case that a single therapy is the best choice across an entire patient population for a given disease. Correspondingly, it is unlikely that naltrexone implants are the best option for all recovering heroin/opiate dependent adults. However, the articles reviewed here suggest that these implants are as or more effective than other therapies currently being offered. Future studies should be done in order to identify patient factors that lead to higher efficacy and lower adverse events with implant therapy. This would allow clinicians to make better decisions as to which patients should be offered this more invasive but effective therapy instead of the traditional oral therapy.

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