



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

## NALTREXONE PELLETS

Naltrexone pellets block the effects of heroin and other opiates when inserted under the skin. They gradually release their medication over time.

500 mg naltrexone pellets that are replaced every two months, and 800 mg naltrexone pellets that are replaced every three months, have been developed and used extensively around the world for over 10 years. Extensive experience, challenge results, serum naltrexone levels, and serum saliva levels have been collected. Licensees are using and providing the naltrexone pellets.

## DISULFIRAM PELLETS

Disulfiram pellets are now available. They use the same patented technology. A 500 mg disulfiram pellet is replaced every 2 months. An 800 mg pellet is still in development.

## INJECTIONS

Naltrexone in oil injections and disulfiram in oil injections now are available from some licensees.

**In the United States**, Lance Gooberman, M.D. makes and uses naltrexone and disulfiram pellets and injections at his office only for his patients at the clinic in New Jersey. However, there are two representatives of Pellet Technologies, L.L.C. who provide naltrexone and disulfiram pellets and injections **outside of the US**. They are Drs. Moran and Surak, and they are located in Hong Kong and Belgrade, Serbia respectively. Contact them:

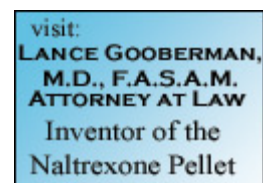
### Hong Kong

Dr. Wayne Moran M.B., B.S.  
 25 Shum Wan Rd.  
 Aberdeen  
 HONG KONG  
 Mobile +852-94887720  
 Office +852-25523108  
 Fax +852-25523117  
 drwayne@netvigator.com  
 www.1212.hk

### Belgrade, Serbia

Gary Surak, M.D.  
 Gersiceva 14A  
 Belgrade 11000, Serbia  
 381-11-241-3536 (office)  
 381-64-237-7018 (cell)  
 The NaltrexZone Serbia

Arrangements for payment can be made to Pellet Technologies, L.L.C. directly or to Drs. Moran or Surak. However, delivery arrangements must be made with Dr. Moran or Dr. Surak.





[Home](#)

[Products](#)

[Patents](#)

[Getting Pellets](#)

[Contact Us](#)

[History](#)

[Legal Issues](#)

## Products

Products consist of intellectual property (trade secrets and patents) directed to:

### Naltrexone pellets

50 mg pellets are replaced every 2 months  
800 mg pellets are replaced every 3 months

### Disulfiram pellets

500 mg pellets are replaced every 2 months  
800 mg pellets are replaced every 3 months

### Naltrexone in oil-3 ml injectable

Single dose bottles of 3 ml  
Multiple dose bottles (10 doses) 30 ml

### Disulfiram in oil-3 ml injectable

Single dose bottles of 3 ml  
Multiple dose bottles (10 doses) 30 m



[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

## PATENTED PROCESS

Pellets from the authorized, licensed pharmacist come with a license for their use to protect providers from charges of contributory infringement of the patents that have claims directed to the use of naltrexone pellets. These patents are:

**US Patent No. 5,789,411**

- Improvements to rapid opioid detoxification

**US Patent No. 6,004,962**

- Rapid opioid detoxification

**US Patent No. 6,203,813**

- Pharmaceutical delivery device and method of preparation therefor

For more information on the inventor of these pellets, please see the Lance Gooberman M.D., J.D., F.A.S.A.M. website.

[Return to top](#)

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[Providers](#)   [Patients](#)

## Getting Pellets

Pellets are legally available in the US only to patients and only at the Addiction Medicine Practice in Merchantville New Jersey.

Pellets are available outside the US to patients and providers from Dr. Wayne Moran in Hong Kong and Dr. Gary Surak in Belgrade, Serbia.



© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

## Contact Us

For more information regarding Pellets or Pellet Technologies, please call Susan Tickner, Manager, at 856.663.4447, or send email to [info@pellettechnologies.com](mailto:info@pellettechnologies.com).

Susan Tickner, Manager  
Lance Gooberman, M.D.,  
Medical Director

One South Centre Street  
Suite 301  
Merchantville, New Jersey 08109

1.800.978.0808  
1.856.663.4447 (phone)  
1.856.488.6380 (fax)

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



- [Home](#)
- [Products](#)
- [Patents](#)
- [Getting Pellets](#)
- [Contact Us](#)
- [History](#)
- [Legal Issues](#)
- [Experience](#)
- [Relapse Rates](#)
- [Fentanyl Challenges](#)
- [Blood Levels](#)
- [Abstract](#)

## Pellet History - Overview

Pellets are pharmaceutical devices inserted under the skin that gradually release a medication over time. The medication is naltrexone. It blocks the effects of heroin and other opiates. It attaches to the brain where the opiates attach, blocking them so they don't cause euphoria. If heroin is used, it passes out of the body with no apparent effect. There is no incentive to continue using the drug.

The pellets have been used as an alternative to incarceration. It enables jails and treatment centers to send patients out with more than an admonishment not to use drugs. It offers the possibility of long term recovery. Naltrexone can protect people while they build a foundation in twelve-step recovery, which teaches them how to live a life without drugs.

A short acting form of the drug, in pill form, has been available for many years. Its safety and effectiveness has been approved by the FDA. However, compliance has always been a problem with the pills. People addicted to drugs simply don't take the medication every day. It is felt that dosing every several months will result in better compliance than daily dosing. Approval is being sought for the long acting pellet. In the meantime the pellets will be available from doctors who have been licensed to make them by Pellet Technologies, L.L.C. The doctors can then implant them in the patients they feel will benefit from the naltrexone.

**Click to View  
the History of Pellets  
as a Slide Show.**

[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[FDA Notes](#)   [FDA Package](#)   [NJ Board](#)   [Liver Toxicity](#)   [Compounding](#)

## Legal Issues

Many legal issues regarding naltrexone pellets have arisen and been overcome.

Meetings were held and opinions written on these issues, including agencies such as the FDA and the NJ Board of Medical Examiners. Included here are documents associated with these events.

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[Injection Procedure](#)   [License](#)

## Providers

We are currently providing services to physicians, for educational as well as business opportunities. Please select [License](#) for more information.

**Physicians:** view the [video](#) for instructions on how to perform the **Pellet Injection Procedure**.

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[Pellet Program](#)   [Eligible Patients](#)

## For Patients

Pellets have been implanted in thousands of patients in the United States and many foreign countries. It involves a simple procedure under a local anesthetic that just takes a few minutes.

If you or a loved one are considering using pellets, please take the time to read the material titled "**Pellet Program**" and "**Eligible Patients.**"

Patients interested in obtaining pellets may contact the following Pellet provider:

The NaltrexZone™

Website: [www.naltrexzone.com](http://www.naltrexzone.com)

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[Experience](#)   [Relapse Rates](#)   [Fentanyl Challenges](#)   [Blood Levels](#)   [Abstract](#)

## Experience

Pellet Technologies has been involved with addiction medicine and the effect of naltrexone on the use of heroin. Some of this experience includes research performed and papers published regarding Pellets vs. Oral Therapy: 30 day Relapse Rates, Fentanyl Challenges, and Naltrexone Blood Levels.

The first pellets were produced in January 1996. The pellets used today were refined in November 2002, and other changes were made in the interim.



© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



- Home
- Products
- Patents
- Getting Pellets
- Contact Us
- History
- Legal Issues
- Experience
- Relapse Rates
- Fentanyl Challenges
- Blood Levels
- Abstract

## Pellets vs. Oral Therapy 30 day Relapse Rates

Lance L. Gooberman MD  
David W. Bradway MD  
Thaddeus Bartter MD

From U. S. Detox, Inc., Merchantville NJ (Drs. Gooberman and Bradway), and from the Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey at Camden (Dr. Bartter)

*Corresponding author: Thaddeus Bartter MD, 3 Cooper Plaza Suite 312, Camden NJ 08103. Tel # (609) 342-2407, Fax # (609) 541-3968*

### Abstract

**Objective.** To evaluate the impact of a depo-naltrexone pellet inserted at time of heroin detoxification upon a 30-day addiction relapse rates

**Design.** A study looking at outcomes for two cohorts of detoxified opiate addicts.

**Setting.** A privately-owned outpatient detoxification center.

**Patients.** 959 patients were detoxified over the study interval. The 665 for whom prolonged follow-up was attempted form the study patients.

**Interventions.** Two post-detoxification opiate blockade methods were used in historical sequence. Initially, oral naltrexone was initiated during detoxification. All patients so treated form cohort 1. This was changed in later cases to the subcutaneous insertion of a depo-naltrexone pellet during detoxification; patients so treated formed the second cohort. Telephone follow-up was performed by a staff member.

**Main outcome measures.** Reported relapse rates for the two cohorts.

**Main results.** For those who responded, the rate of relapse to regular drug use at 30 days was 33.2% for patients treated with oral naltrexone versus only 0.6% for the depo-naltrexone group ( $p < 0.0001$ ). If all patients for whom follow-up was attempted but not sustained for 30 days were assumed to have relapsed to opiate usage, a method which would bias the results against efficacy, the rate of relapse would have been 53% for the oral naltrexone group versus 28% for the depo-naltrexone group, still significant at a  $p < 0.001$  despite the bias.

**Conclusions.** Depo-naltrexone is effective in preventing early relapse and can allow more time after detoxification during which interventions can be instituted to help an addict to sustain abstinence.

In 1897, MaCleod reported that withdrawal from opiates could be attained "...within three days without

suffering." This was accomplished by the accidental administration of heavy sedation with bromide. Two years later, MacLeod reported the intentional use of sedation with bromide to facilitate withdrawal.<sup>2</sup> The procedure was not without its risks,<sup>2</sup> and the idea disappeared from the literature for almost 100 years. Around 1977, opiate antagonists, initially used as antidotes for heroin overdoses, began to be used to accelerate opiate detoxification.<sup>3</sup> This led to efforts to decrease the intensity of this compacted withdrawal; several refinements in the management of precipitated withdrawal evolved over the next 12 years, including the use of sedatives.<sup>4-8</sup> Management of withdrawal culminated in rapid opiate detoxification under general anesthesia.<sup>9</sup> This process, too, has been refined over the past several years. It is now possible to effect opiate detoxification and blockade over a period of several hours with minimal patient discomfort.<sup>10,11</sup> This is a highly effective technique with a short-term success rate of 100%; patients who ask for the procedure are sedated and awake hours later completely detoxified.

Although rapid opiate detoxification represents an exciting advance in the treatment of opiate dependence, it is obvious that the goal of treatment is not only detoxification but sustained maintenance of abstinence. Naltrexone (NTX) is an orally available opiate antagonist which effectively ablates opiate effect when taken regularly. This need for regular dosing has, however, limited its clinical utility for patients post-detoxification. We report a series of 655 patients, contrasting 30-day abstinence rates for those treated with oral naltrexone (O-NTX) with abstinence rates for those treated with a long-acting subcutaneous depo-naltrexone (D-NTX) preparation. This preparation appears to have promise for the prevention of relapse after detoxification.

## Methods

Between March, 1995 and October, 1997, 959 patients underwent opiate detoxification under general anesthesia. All subjects had requested rapid opiate detoxification.<sup>12</sup> The inclusion criterion was active opiate dependence. Exclusion criteria were (1) history of cardiac arrhythmia, myocardial infarction or decreased left ventricular function (2) pregnancy, and (3) age greater than 65 years. All procedures were performed in a private outpatient setting.<sup>12</sup>

The treating physician, in the presence of a caretaker selected by the patient, explained the procedure to the patient. After explanation, a detailed written consent form was signed prior to detoxification.

History and physical examination was followed by the initiation of continuous monitoring of temperature, electrocardiogram, blood pressure, and pulse oximetry (with exhaled carbon dioxide levels monitored after intubation). If all parameters fell within normal limits, anesthesia was induced. The patients were intubated and placed on a ventilator. When the airway was secure, neuromuscular blocking agents were administered to maintain paralysis. Withdrawal was then precipitated with a narcotic antagonist. The patients were maintained under general anesthesia for 3-6 hrs, during which time naltrexone maintenance therapy was initiated. Patients were then brought out of anesthesia and extubated. An observation period followed extubation, during which time patients were assisted to the bathroom and in dressing. Patients were required to ambulate a distance of at least 300 ft. prior to discharge. Two short-term post-detoxification procedures were utilized. First, the caretaker who accompanied the patient to the detoxification had agreed a priori to stay with the patient for 48 hours after detoxification. Second, physician follow-up was attempted for all patients in the 72 hours following detoxification. In many cases, there was an attempt at sustained follow-up by an office staff member. The patients for whom sustained follow-up was attempted form the subjects of this report.

Starting in November of 1996, the detoxification included the subcutaneous implantation of D-NTX; the pellet was inserted prior to termination of anesthesia. The initial pellets totaled 600 mg with the dose later increased to 1000 mg/pellet. (Bartter & Gooberman, submitted for publication) These two subsets are joined in the analyses described below. This change to the routine use of D-NTX allows division of the population into two groups, those maintained on oral naltrexone post detoxification, the O-NTX group, and the D-NTX group. This study focuses upon the comparison of these groups with respect to opiate relapse. T-testing was used for between-group comparisons, with a  $p < .05$  considered significant.

## Results

Of the 959 total detoxifications, office staff made at least one contact with 655 in an effort to continue with sustained follow-up. (Sustained follow-up was not possible in all cases.) Those 655 patients were divided into O-NTX and D-NTX groups. There were 487 men and 168 women, with a mean age of 36 (range, 19-62). Out of the 665 patients, 432 were treated with O-NTX and 223 were treated with D-NTX. Three hundred and four

(70.4%) of the O-NTX subjects had follow-up for at least 30 days, and 162 (72.6%) of the D-NTX patients had follow-up for at least 30 days. The breakdown is represented in Figure 1.

Exhaustive review of the demographics of the O-NTX and D-NTX subjects is presented in Table 1. There were only two significant differences between the two groups. First, the mean age of the O-NTX group, 37.1, was slightly greater than 34.9, that of the D-NTX group. Second, the duration of follow-up was longer for the O-NTX group. Average follow-up for the O-NTX group was 97.4 days, with a range of 1 to 780 days. Average follow-up for the D-NTX group was 74.3 days, with a range of 1 to 412 days. The following were compared and shown not to be significantly different between groups: opiate or combination of opiates used prior to detoxification, and amount of opiate used. These were looked at for the total O-NTX and D-NTX groups and then broken down by gender within each group, with no differences between groups for any breakdown (see Table 1).

The 30-day reported relapse results for the two populations were significantly different. Of the 304 patients in the O-NTX group for whom 30-day follow-up was available, 66.8% (203) stated that they were not using opiates, while 33.2% (101) admitted relapse to regular opiate usage. For 162 patients in the D-NTX group for whom 30-day follow-up was available, 99.4% (161) stated that they were not using opiates, while one patient admitted to relapse. The difference is highly significant ( $p < 0.0001$ ). It is important to note that patients who were not using at day 30 may have tried opiates sporadically and abandoned them due to lack of efficacy. The distinction here is between those who had relapsed to regular usage versus those who had not reverted to addictive drug-taking; patients who tried opiates but did not relapse to regular use are in the "non-user" category in this study. The study is thus designed as an outcome study looking not at the effect of NTX upon craving or initial behavior, but rather at the most crucial outcome, presence or absence of relapse.

Since a significant number of patients in both populations were not successfully followed for 30 days (128 for the O-NTX and 61 for the D-NTX population), the argument could be made that the reason that they could not be contacted was that they had relapsed. Although this assumption is biased against the efficacy of D-NTX, the numbers would be as follows given the assumption: a non-relapse rate of 47% in the O-NTX group versus 72% in the D-NTX group ( $p < 0.001$ ).

There were no significant differences in non-usage and relapse rates within populations for men versus women. For the O-NTX population, there was a 30-day abstinence rate of 66.2% ( $n=147$ ) for men versus 68.2% ( $n = 56$ ) for women; and for the D-NTX population, men had a abstinence rate of 99.2% ( $n=124$ ) versus 100% ( $n=38$ ) for women. The same-gender results between O-NTX and D-NTX groups were highly significant for both men ( $p < 0.001$ ) and women ( $p = 0.0003$ ). Similarly, gender-based statistics given the assumption that all patients not followed for at least 30 days had gone back to regular opiate usage remained significant for between-group comparisons.

When the populations were broken down by choice of opiates, non-relapse rates remained significantly greater for all D-NTX groups for which numbers were large enough to allow valid statistical analysis. For those using exclusively heroin, the non-relapse rates were 68.2% ( $n=192$ ) for the O-NTX population versus 99.0% ( $n=103$ ) for the D-NTX population ( $p < 0.0001$ ). For the combination of heroin plus methadone, the non-relapse rates were 60.7% ( $n=84$ ) for the O-NTX population and 100.0% ( $n=33$ ) for the D-NTX population ( $p < 0.0001$ ). There were not enough patients to demonstrate a significant difference using the same tests of statistical significance in the exclusive methadone users or the users of "other opiate combinations." (The exclusive methadone results are 73.6% ( $n=19$ ) for O-NTX, and 100% ( $n=18$ ) for the D-NTX populations. The exclusive "other opiates" results were 77.7% ( $n=9$ ) for the O-NTX, and 100% ( $n=7$ ) for the D-NTX population.)

## Discussion

This study documented reported 30-day relapse rates after detoxification for patients receiving oral naltrexone maintenance (the O-NTX group) and patients receiving subcutaneous depo-naltrexone (D-NTX). The results were statistically very significant in favor of D-NTX. They stayed significant even when all patients lost to sustained follow-up were assumed to have resumed active opiate usage, an assumption which would bias results against any such significance.

The weaknesses of the study are obvious; the study was retrospective, only 68% of the patients detoxified over the study interval were included in the study, and the results were obtained by telephone follow-up. Yet the groups in the O-NTX and D-NTX groups were remarkably similar, both groups were approached similarly with no evident reason why one population would lie about active opiate usage and the other group not lie, and the statistical significance of the findings was large enough to tolerate considerable error without losing

significance. This is evidenced by the results given the assumption that all patients not followed for 30 days had resumed opiate usage. (In fact, one reason for loss of follow-up was limitations in office staff, not a documented inability to reach patients.)

There were two differences between the O-NTX and D-NTX groups. One was a decreased mean age for the D-NTX group, 34.9 versus 37.1 for the O-NTX group. The implication is that the mean age of opiate users is decreasing, a distressing implication. There is no obvious way in which this age difference could have biased the results. The second difference was the mean follow-up, which is greater for the O-NTX group since the two groups were studied in sequence and not simultaneously; there was a longer available time for the O-NTX patients to have been followed. The 30-day point used in this report ablates the meaning of that difference for this study.

One patient, the single patient in the D-NTX group who reported resumption of opiate usage, was studied further, as he reported getting high on opiates whereas prior work with D-NTX had suggested that this should not be possible. (Bartter and Goberman, submitted for publication.) He asked for repeat detoxification and agreed to come into the office for testing. He was challenged twice. First, he was given a challenge of 250 mcg of intravenous Fentanyl (morphine equivalent, approximately 20 mg).<sup>13</sup> There were no pupillary changes, respiratory changes, or mental status changes. He was then given an intravenous challenge of 4 mg of naloxone. There were no signs of withdrawal. The interesting implication is that the patient had remained fully blocked by his D-NTX pellet and that his reported highs from heroin did not represent a physiologic response.

NTX has been shown to be of significant benefit post-detoxification in "controlled" populations such as prisoners. Brahen et al. used the certain blocking effect of NTX to allow previously opiate-addicted prisoners willing to take NTX access back to the community in a work-release program.<sup>14</sup> They documented the efficacy of this program over a 10-year period. Chan, working in Singapore where all known addicts are detained by executive order, also used NTX in a work-release program and noted a 1-year sobriety rate of 76.3% after initiating a NTX program versus a 24% 1-year sobriety before NTX.<sup>15</sup> Cornish, in a study of parolees with a history of opiate abuse demonstrated 46% fewer re-incarcerations in a subset of parolees who agreed to take oral NTX.<sup>16</sup> The majority of the drop-outs in this study occurred during the first month, a time during which D-NTX would have rendered opiates ineffective. Unfortunately, the clinical efficacy of NTX in more controlled populations has not held true for patients outside of such environments.

The concept of sustained-release NTX is not new. A sustained-release naltrexone preparation that blocks the effects of narcotics for about a month has been a goal of NIDA since the 1980s and is the subject of several publications.<sup>17-19</sup> These early efforts did not come to fruition in the form of a readily available preparation. We have now had extensive experience with our preparation. (Goberman and Bartter, submitted for publication) To our knowledge, this is the first report looking at the effect of such a preparation upon sustained abstinence rates.

No adjunct to the process of treating a chronic relapsing problem should be considered a "cure." Abstinence is not an event; it is a sustained process which includes motivation, detoxification, and social/emotional interventions perhaps best achieved with a 12-step program. The goal of D-NTX is narrow; its goal is to allow more time after detoxification during which other interventions might be instituted without being derailed by recurrent intoxication.

In conclusion, D-NTX has been shown to demonstrate success in helping addicts avoid relapse for at least 30 days after a rapid opiate detoxification. The data support the insertion of D-NTX as a standard part of the detoxification procedure. The battle against opiate dependence has been too arduous and disappointing for us to make dramatic claims about the use of D-NTX. It does, nonetheless, appear to be yet another step which may help an addict towards sobriety.

## References

1. Macleod N. Morphine habit of long standing cured by bromide poisoning. *Br Med J* 1897;i:76-77
2. Macleod N. Cure of morphine, chloral hydrate, and cocaine habits by sodium bromide. *Br Med J* 1899;i:896-898
3. Resnick R, Kestenbaum R, Washton A, Poole D. Naloxone-precipitated withdrawal: a method for rapid

induction onto naltrexone. Clin Pharmacol Therap 1977;21:409-413

4. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine. JAMA 1980;243:343-346
5. Gold MS, Pottash ALC, Sweeney DR, Kleber HD. Effect of methadone dosage on clonidine detoxification efficacy. Am J Psych 1980;137:375-376
6. Gold MS, Pottash AC, Sweeney DR, Extein I, Annitto WJ. Opiate detoxification with lofexidine. Drug Alc Dependence 1981;8:307-315
7. Kleber HD, Topazian M, Gaspari J, Riordan CE, Kosten T. Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. Am J Drug Alcohol Abuse 1987;13:1-17
8. Vining E, Kosten TR, Kleber HD. Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. Br J Addiction 1988;83:567-575
9. Presslich O, Loimer N. Opiate detoxification under general anesthesia by large doses of naloxone. Clin Toxicol 1989;27:263-270
10. Brewer C. Ultra-rapid, antagonist-precipitated opiate detoxification under general anesthesia or sedation. Addiction Biology 1997;2:291-302
11. Simon DL. Rapid opioid detoxification using opioid antagonists: history, theory and state of the art. J Addictive Dis 1997;16:103-122
12. Bartter T, Gooberman LG. Rapid Opiate Detoxification. Am J Drug Alcohol Abuse 1996;22:489-495
13. Hardman JG, Goodman AG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw Hill: 543
14. Brahen LS, Brewer C. Naltrexone in the Criminal Justice System. In Brewer C, Ed. Treatment Options in Addiction; Medical Management of Alcohol and Opiate Abuse London:Gaskell, 1993; 46-53
15. Chan KY. The Singapore naltrexone community-based project for heroin addicts compared with drugfree community-based program: the first cohort. J Clin Forensic Med 1996;3:87-92
16. Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, and O'Brien CP. Naltrexone pharmacotherapy for opioid dependent federal probationers. J Substance Abuse Treatment 1997;14:529-534
17. Chiang CN, Hollister LE, Kishimoto A, Barnett G. Kinetics of a naltrexone sustained-release preparation. Clin Pharmacol Ther 1984;36:704-708
18. Chiang CN, Hollister LE, Gillespie HK, Foltz RL. Clinical evaluation of a naltrexone sustained-release preparation. Drug Alcohol Dependence 1985;16:1-8
19. Sharon AC, Wise DL. Development of drug delivery systems for use in treatment of narcotic addiction. In Wilette RE and Barnett G, eds. Naltrexone: Monograph 28, National Institute on Drug Abuse, 1980. pp. 194-213

**Table 1. PATIENT DEMOGRAPHICS**

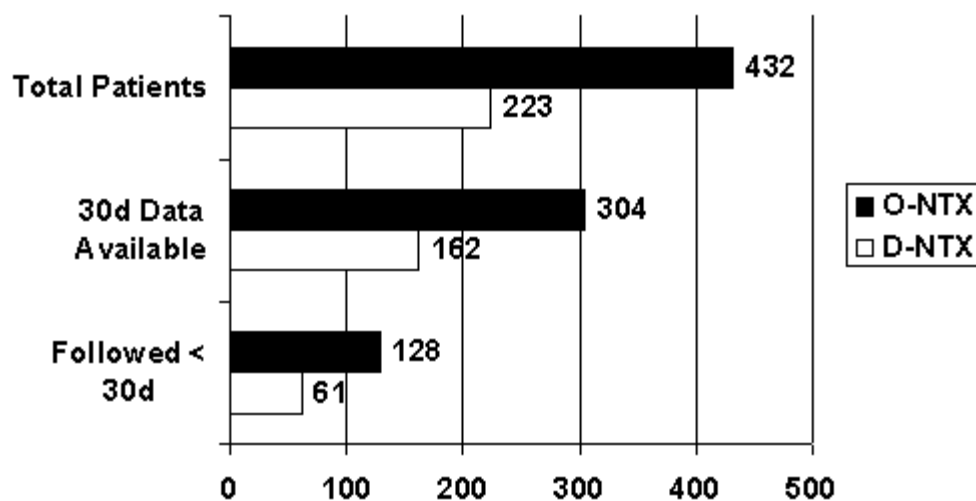
	<b>O-NTX</b>	<b>D-NTX</b>	<b>p</b>
<b>Total Patients Studied</b>	432	223	

<b>Men, n (%)</b>	324 (75.0%)	163 (73.1%)	NS
<b>Women, n (%)</b>	108 (25.0%)	60 (26.9%)	NS
<b>Mean Age <math>\pm</math> SD (range)</b>	37.1 $\pm$ 8.5 (19-62)	34.9 $\pm$ 9 (19-59)	> .05
<b>Mean Duration of Follow-Up (range)</b>	97 (1-780)	74 (1-412)	> .05
<b>Exclusive Heroin Users, n (%)</b>	273 (63.2%)	148 (66.4%)	NS
<b>Heroin, bags (range)</b>	10.2 $\pm$ 10.3 (1-100)	8.8 $\pm$ 7.5 (1-60)	NS
<b>Exclusive Methadone Users, n (%)</b>	37 (8.6%)	18 (8.1%)	NS
<b>Methadone, mg (range)</b>	77 $\pm$ 52 (8-300)	75 $\pm$ 63 (15-270)	NS
<b>Combo Heroin + Methadone Users, n (%)</b>	109 (25.2%)	38 (17.0%)	NS
<b>Heroin, bags (range)</b>	9.2 $\pm$ 12.1 (1-100)	7.6 $\pm$ 7 (1-40)	NS
<b>Methadone, mg (range)</b>	56 $\pm$ 60 (1-400)	54 $\pm$ 33 (1-100)	NS
<b>Other Opiate Combinations, n (%)</b>	13 (3.0%)	19 (8.5%)	NS
<b>OPIATE CHOICE BY GENDER</b>			
<b>Male Exclusive Heroin Users, n (%)</b>	209 (48.4%)	109 (48.9%)	NS
<b>Female Exclusive Heroin Users, n (%)</b>	64 (14.8%)	39 (17.5%)	NS
<b>Male Exclusive Methadone Users, n (%)</b>	25 (5.8%)	13 (5.8%)	NS
<b>Female Exclusive Methadone Users, n (%)</b>	12 (2.8%)	5 (2.2%)	NS

<b>Male Heroin + Methadone Users, n (%)</b>	80 (18.5%)	29 (13.0%)	NS
<b>Female Heroin + Methadone Users, n (%)</b>	29 (6.7%)	9 (4.0%)	NS
<b>Male Other Opiate Combinations, n (%)</b>	10 (2.3%)	12 (5.2%)	NS
<b>Female Other Opiate Combinations, n (%)</b>	3 (0.7%)	7 (3.1%)	NS

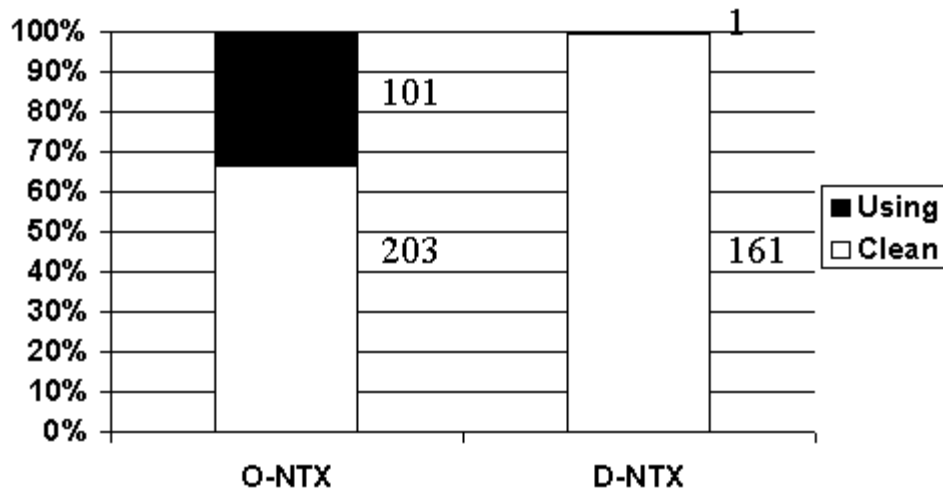
**Figure 1.** Breakdown of study population.

## Study Population



**Figure 2.** Opiate use at 30 days.

# Reported Opiate Use at 30 Days



[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[Experience](#)   [Relapse Rates](#)   [Fentanyl Challenges](#)   [Blood Levels](#)   [Abstract](#)

## Fentanyl Challenges

Lance L. Gooberman, MD  
Thaddeus Bartter, MD, FCCP

From U. S. Detox, Inc., Merchantville NJ (Dr. Gooberman), and from the Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey at Camden (Dr. Bartter)

*Reprint requests: Dr. Lance Gooberman, One South Centre Street, Merchantville, NJ 08109*

Corresponding author: Dr. Gooberman, telephone (856) 663-4447, fax (856) 488-6380, e-mail lgooberman@gmail.com

### Abstract

This report describes effective prolonged opiate blockade by subcutaneous depot-naltrexone (d-NTX) preparation. The d-NTX is a 1000 mg pellet inserted at opiate detoxification. The assay of effective opiate blockade was direct opiate challenge. Fifteen challenges were performed. Opiate challenges occurred from 21 to 70 days after d-NTX implantation (mean 40.9 days). All patients were refractory to the opiate. The data suggest that this d-NTX preparation is effective for at least 4 weeks after implantation. While not a "cure" for opiate dependence, d-NTX may allow a prolonged interval after detoxification during which addicts will have time to benefit from social/psychological interventions.

Naltrexone (NTX) is a potent and effective narcotic antagonist.(1) People with drug levels  $\geq 1$  ng/ml are refractory to the effects of intravenous opiates,(2) and it has potential efficacy as an adjunct to help maintain abstinence in opiate addicts after detoxification. Naltrexone was discovered in the late 1960s and evaluated at some length in the 1970s.(1,3) After it aroused clinical excitement in the early 1970s, however, its potential efficacy met two major barriers. First, patients had to be completely detoxified before NTX can be started, as dosing an active opiate user will lead to full-blown and accelerated withdrawal.(4) Second, although it is orally available and has a longer duration of effect than the other available narcotic antagonists, oral NTX still needs to be given a minimum of three times a week, making compliance an issue.(5) We feel that the first issue has a solution in the use of accelerated opiate detoxification under sedation or anesthesia.(6) The second issue may have a solution in the use of slow-release subcutaneous depot-NTX (d-NTX).

Early recognition of the issue of compliance with oral NTX after detoxification led to some initial work in the development and evaluation of d-NTX preparations,(2,7-10) but the surge of interest apparent in the 1970s has not yet led to a published study demonstrating the effective use of d-NTX in a clinical setting. This report describes such a clinical experience.

### Methods

Detailed written consent was obtained from every patient before any intervention. Consents were obtained for precipitated withdrawal and for pellet insertion.

All patients were initially detoxified under anesthesia, with propofol the principle anesthetic.(6) After induction with the propofol, patients were intubated and paralyzed. Withdrawal was then effected via administration of opiate receptor blockade with opiate antagonists. Pellet insertion occurred before the patient awoke from anesthesia.

All patients described herein were treated with pellets of NTX mixed with pharmacologically acceptable excipients and compressed into a cylindrical form. The preparation was a single pellet which contained 1000 mg of NTX in a cylinder 12.5 mm in diameter 9.5 mm high. Insertion involved a small incision and subcutaneous deposition of the pellet approximately 3.5 cm away from the incision site using blunt dissection of the subcutaneous tissues. Some patients later returned for repeat pellet insertion approximately two months later. In these cases, the insertion was performed using lidocaine with 1/1000 epinephrine.

Initial assay attempts involved NTX blood levels from different commercial laboratories, but the blood levels appeared not to correlate with clinical experience; patients who reported being refractory to street-taken opiates had unmeasurable levels at the time. This could have been due to levels below the sensitivities of the assays but nonetheless clinically effective, due to degradation of the NTX or its metabolites prior to assay, or it could have been due to errors in testing. Because of these issues, the assay was changed to a classic clinical assay of efficacy, direct opiate challenge.(1-3) Fentanyl was used as the challenge agent.

Fifteen challenges were performed on ten d-NTX recipients. One patient had three challenges, 3 had two challenges, and the remaining 6 had one challenge each. Of the fifteen challenges, 9 were given to men and 6 to women. One patient, patient four, had one challenge after each of two successive d-NTX insertions. In the other cases with more than one challenge, all were done after a single pellet insertion. The mean age of the patients being challenged was 30.3 with a range of 19 to 39. Patients were challenged with 250 mcg of fentanyl, a synthetic opioid with approximately 80 times the potency of morphine.(11) It has a short duration of action,(11) making it a good candidate for opiate challenge. The dose given was the pharmacologic equivalent of a 20 to 25 mg bolus of morphine.

## Results

The results of the fentanyl challenges are presented in table 1. Challenges were performed a mean of 40.9 days after implantation of the 1000 mg tablet, with the earliest challenge at day 21 and the latest at day 70. As can be seen, no patient had a significant response. After fentanyl challenge, there were no significant changes in pupillary size or respiratory rate despite the significant narcotic load. In patient nine, there was a subjective impression of slight pupillary change which, if present, was too slight to be reflected in a change in measured pupillary size. The most significant adverse event after Fentanyl administration was what appeared to be a vasovagal response in patient five which was short-lived and not accompanied by evidence of opiate intoxication.

## Discussion

Using fentanyl challenge, clinical efficacy of d-NTX has been demonstrated in a small group of patients for up to 70 days after implantation of a single 1000 mg NTX pellet. No patient demonstrated any evident response to direct opiate challenge.

While the times after pellet insertion at which Fentanyl challenge was performed varied, the data strongly suggest that the d-NTX pellet provides effective opiate receptor blockade for at least 4 weeks in most subjects. This duration is potentially crucial, as it would allow more time for post-detoxification programs to be effective. In the absence of opiate blockade, the highest relapse rate after detoxification occurs within the month following detoxification,(12) a time during which the patients described herein were refractory to opiate effect. Note that an alternative approach, maintenance therapy, has not been an obvious answer to the problem of relapse; even maintenance has high recidivism rates, with failure rates of 66% within the first month of treatment using high-dose levomethadyl acetate (LAAM) the best of the results reported in a recent study.(13)

This is not the first attempt at development of a subcutaneous, slow-release form of NTX. As mentioned, several articles in the early 1980s described the manufacture of NTX-containing pellets and of their biological release in both animals and human beings. (2,7-10) This form of subcutaneous d-NTX was demonstrated to give a promising release profile with reasonable drug levels, and prolonged resistance to opiates in both human and non-human subjects after implantation was demonstrated.(2,7-10) Work with these preparations tapered off after the mid-1980s. We posit three reasons for this tapering. First, the system used for the preparation of pellets in those studies was protracted and expensive. Second, the methods described involved injectable preparations that could not be removed, in contradistinction to the pellets used for this study, which can be

removed in any emergent situation. A third possibility is that incomplete detoxification made it difficult to initiate NTX therapy. To our knowledge, this is the first description of ongoing clinical experience with any d-NTX preparation.

One other experience with the d-NTX tablets used in this study has been reported. Brewer and Gastfriend placed successive d-NTX tablets in a young heroin addict after an initial detoxification.(14) The second tablet was placed five weeks after the first. Two weeks after the second implant, the patient was given a double challenge. First he was challenged with intravenous fentanyl in 50 mcg increments until a total of 1000 mcg had been given (roughly equivalent to 80 mg of morphine). There was no subjective or objective change. The same subject was then given 0.4 mg of intravenous naloxone and 50 mg of oral NTX. Again, there was no change. The data are consistent with the findings reported herein.

It is important to note that d-NTX did not prevent experimentation with street drugs post-detoxification. It did prevent a slip from becoming a relapse. This allows a longer period for meaningful intervention.

The patients given fentanyl challenge and reported herein represent only a fraction of those in whom pellets have been inserted in the last 2 years. From that experience, the only complication of d-NTX implantation which has occurred with frequency has been inflammation at the insertion site. A local response at the insertion sites is relatively common (~15%), although very few of the events (~1.3%) appear to be infectious and none have required more than oral antibiotic therapy and local soaks/dressings. Of note, earlier animal studies with a different d-NTX preparation have demonstrated that individual animals exhibited a non-necrotic inflammatory response which appeared to be caused by the NTX itself..(10) This is probably the same inflammatory response seen in our patients, and it may even play a positive role in the effective slow absorption over time reflected in the clinical efficacy of the d-NTX preparation. No systemic side-effects have been reported by any d-NTX patient. This is not surprising, as drug levels from the slow release of the subcutaneous NTX would be significantly lower than those obtained by oral administration,(2,7,15) and even orally administered drug has minimal side-effects.(16,17,18)

We would argue that maintenance of abstinence with d-NTX is more rational than maintenance of opiate dependence with a long-acting opiate such as Methadone. There are, however, several potential problems with NTX which need to be acknowledged. First, a patient with active NTX blockade will not be susceptible to routine narcotic analgesia for emergent situations. One d-NTX patient needed surgery for an arm fracture while he had a NTX pellet in place, and non-narcotic analgesia needed to be provided. Another patient developed symptomatic cholelithiasis with a d-NTX pellet in place and underwent laparoscopic cholecystectomy with non-steroidal analgesics for pain control. She was able to maintain abstinence throughout the process. Second, the effects of NTX on pregnancy have not been established. While one could argue that it may be safer to administer tiny doses of NTX via a slow-release system than to allow intermittent opiate usage during pregnancy, there is no available clinical information which one can use to apportion risk. This clinical issue needs desperately to be addressed. Third, the use of subcutaneous deposition does require an invasive technique, albeit minor.

We must emphasize that rapid detoxification coupled with d-NTX is not curative. Even if d-NTX is effective for up to 70 days, it is not a "solution" to drug dependence. We believe that all detoxifications need to be accompanied by attempts at social support and social change, such as a 12-step program. D-NTX is not that therapeutic environment; d-NTX is an adjunctive therapy whose goal is to give patients who are capable of change the opportunity to change over an extended interval during which drug-taking will not renew physical dependence.

In summary, we have described the use of a subcutaneous NTX pellet inserted at the end of detoxification which is capable of blocking opiate responses for extended periods after implantation. We believe that the use of this pellet may be a valuable adjunct to the process of helping addicts to break the vicious cycle of opiate dependence.

## References

1. Martin WH, Jasinski DR, Masky PA. Naltrexone, an antagonist for the treatment of heroin dependence. *Arch Gen Psych* 1973;28:784-791
2. Chiang CN, Hollister LE, Gillespie HK, et al. Clinical evaluation of a naltrexone sustained-release preparation. *Drug Alcohol Dependence* 1985;16:1-8
3. Verebey K, Volavka J, Mule SJ, et al. Naltrexone: disposition, metabolism, and effects after acute and

- chronic dosing. Clin Pharm and Therapeutics 1976;20:318-327
4. Tornabene VW. Narcotic withdrawal syndrome caused by naltrexone. Ann Intern Med 1974;81:785-787
  5. Brahen LS, Brewer C. Naltrexone in the Criminal Justice System. In Brewer C, Ed. Treatment Options in Addiction; Medical Management of Alcohol and Opiate Abuse London: Gaskell, 1993; 46-53
  6. Bartter T, Gooberman LG. Rapid Opiate Detoxification. Am J Drug Alcohol Abuse 1996;22:489-495
  7. Chiang CN, Hollister LE, Kishimoto A, et al. Kinetics of a naltrexone sustained-release preparation. Clin Pharmacol Ther 1984;36:704-708
  8. Harrigan SE, Downs DA. Pharmacological evaluation of narcotic antagonist delivery systems in Rhesus monkeys. In Willett RE, Barnett G, eds. Narcotic Antagonists: Naltrexone Pharmacology and Sustained-Release Preparations, NIDA research monograph 28, DHHS publication no. 81-902, Washington D.C., 1980:77-92
  9. Reuning RH, Liao SHT, Staubus AE, et al. Pharmacokinetic quantitation of naltrexone controlled release from a copolymer delivery system. J Pharmacokin Biopharm 1983;11:369-387
  10. Yamaguchi K, Anderson JM. Biocompatibility studies of naltrexone sustained release formulations. J Controlled Release 1992;19:299-314
  11. Hardman JG, Goodman AG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw Hill:543
  12. Kleber HD, Kosten TR. Naltrexone induction: psychologic and pharmacologic strategies. J. Clin Psychiatry 1984;45:29-38
  13. Eissenberg T, Bigelow GE, Strain EC, et al. Dose-related efficacy of levomethadyl acetate for treatment of opioid dependence. JAMA
  14. Brewer C, Gastfriend DR. Letter to the editor. JAMA 1998;279:1872-1997;277:1945-1951
  15. Wall ME, Brine DR, Perez-Reyes M. Metabolism and disposition of naltrexone in man after oral and intravenous administration. Drug Metab Dispos 1981;9:369-375
  16. Cornish JW, Henson D, Levine S, et al. Naltrexone maintenance; effect on morphine sensitivity in normal volunteers. Am J Addictions 1993;2:34-38
  17. Renault PF. Treatment of heroin-dependent persons with antagonists: current status. In Willett RE, Barnett G, eds. Narcotic Antagonists: Naltrexone Pharmacology and Sustained-Release Preparations, NIDA research monograph 28, DHHS publication no. 81-902, Washington D.C., 1980:11-22
  18. Brahen LS, Capone T, Capone D. Naltrexone: lack of effect on hepatic enzymes. J Clin Pharmacol 1988;28:64-70

Table 1. **Responses to Fentanyl Challenge**

Challenge #	Pt #	Age	Sex	Days post implant	Pupillary size pre/post challenge	Respiratory Rate pre/post challenge	Subjective Response
1	1	36	M	34	2-3/2-3	20/20	none
2	1	36	M	60	2-3/2-3	20/20	none

3	1	36	M	70	2-3/2-3	20/20	none
4	2	30	M	30	2-3/2-3	18/18	none
5	2	30	M	35	2-3/2-3	20/20	none
6	3	36	F	37	3-4/3-4	16/18	slight dizziness, lightheaded 1 minute post injection
7	3	36	F	36	2-3/2-3	20/20	none
8	4	22	F	44	2-4/3-4	16/14	none
9	4	22	F	41	3/3	18/18	none
10	5	33	F	38	2-3/2-3	16/16	none
11	6	28	F	49	2-3/2-3	20/20	lightheaded
12	7	28	M	49	2-3/2-3	20/20	nausea, possible vagal response
13	8	39	M	38	2-3/2-3	16/20	none
14	9	19	M	32	3-4/3-4	16/16	slight dizziness, slight pupillary change
15	10	32	M	21	2-3/2-3	16/16	none

July 30, 1998

Sheldon I. Miller, MD, Editor  
*The American Journal on Addictions*  
 7301 Mission Road #252

Prairie Village, KS 66208

Re: Depot Naltrexone (d-NTX) for Protection Against Opiate Effect in the Post-Detoxification Period

Dear Dr. Miller:

We appreciate the request for manuscripts sent to Dr. Gooberman after the Toronto meeting of the American Psychiatric Society. In response, we have prepared this manuscript, which covers an aspect of the detoxification work being done out of U.S. Detox, Inc. We have in addition submitted an abstract covering this material for the 9<sup>th</sup> annual AAAP meeting. The material has not been published elsewhere and is not being considered for publication elsewhere. We understand and appreciate the fact that your request for submission does not in any way obviate the need for peer review. We look forward to hearing the comments and critiques of your reviewers.

Sincerely,

---

Lance Gooberman, MD

---

Thaddeus Bartter, MD

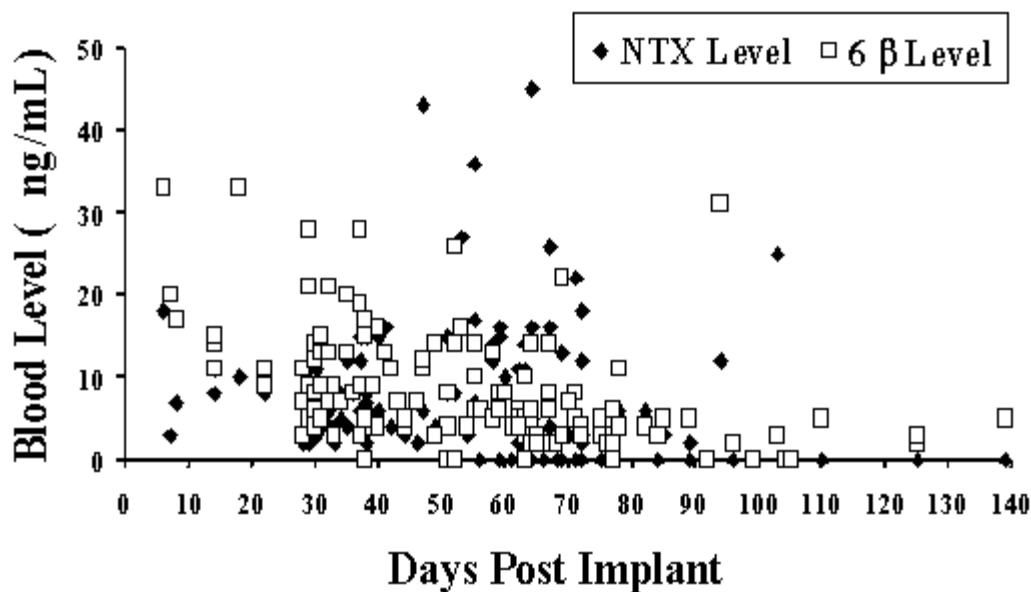
[Return to top](#)



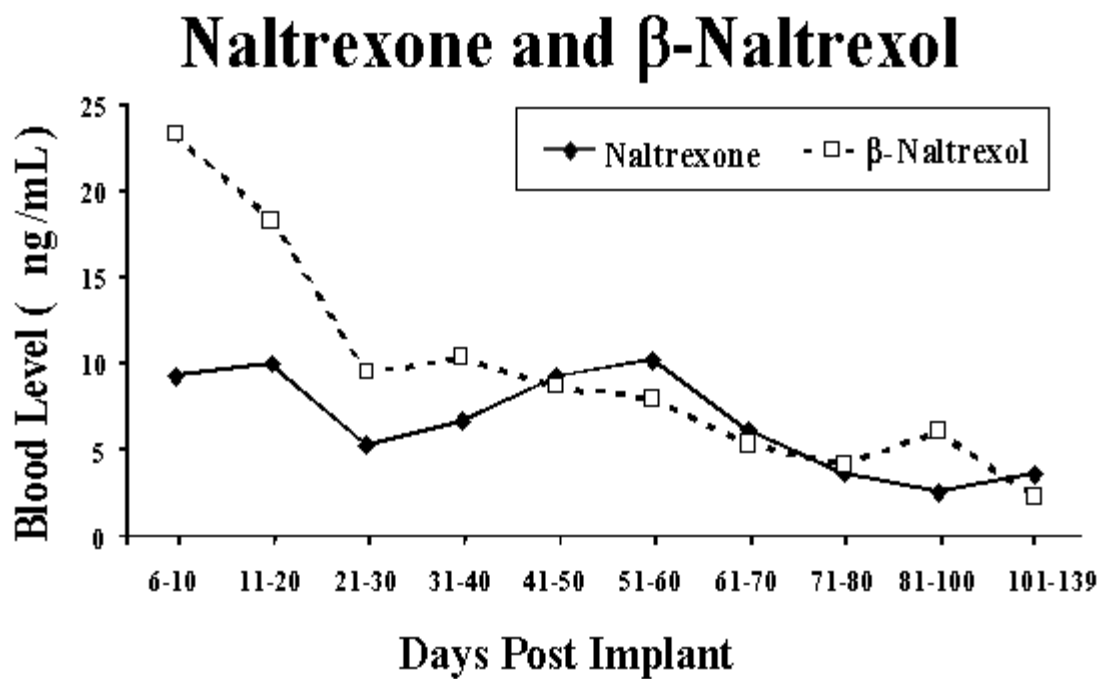
[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[Experience](#)   [Relapse Rates](#)   [Fentanyl Challenges](#)   [Blood Levels](#)   [Abstract](#)

## BLOOD LEVELS

### Naltrexone and $\beta$ -Naltrexol



Days Post Implant	Naltrexone	$\beta$ -Naltrexol	Number
6-10	9.3	23.3	3
11-20	10.0	18.3	4
21-30	5.3	9.5	15
31-40	6.7	10.4	28
41-50	9.3	8.7	10
51-60	10.2	8.0	18
61-70	6.2	5.4	28
71-80	3.7	4.2	17
81-100	2.6	6.1	9
101-139	3.6	2.3	7



[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[Experience](#)   [Relapse Rates](#)   [Fentanyl Challenges](#)   [Blood Levels](#)   [Abstract](#)

## DETERMINATION of NALTREXONE and ITS MAJOR METABOLITE 6- $\beta$ -NALTREXOL in SAMPLES from HEROIN ADDICTS on NALTREXONE IMPLANTS TREATMENT

**L.Olsen, A.S. Christophersen**

National Institute of Forensic Toxicology, P.O. Box 495 Sentrum 0105 Oslo, Norway

A sensitive and specific high-performance liquid chromatographic (HPLC) method combined with electrochemical (EC) and UV detection has been modified\* and validated for the analyses of naltrexone and its major metabolite 6- $\beta$ -naltrexol in plasma. The analytical procedure includes liquid/liquid extraction with dichloromethane/isopropanol (19:1) after alkalinizing (pH 9), back-extraction in phosphoric-acid (0,017 M) and direct injection on a Guard column, 10 x 2 mm, which was coupled to Spherisorb 3 ODS-2, 100 x 4,6 mm, 3 mm, as analytical column, 40°C, connected to both EC - and UV-detector. Acetonitrile (28%)/phosphoric acid (40mM)/ SDS (2mM) was used as mobile phase, flowrate 0.8 ml min Ketobemidon was used as internal standard (IS). The recovery was found to be approximately 80% for both naltrexone, 6- $\beta$ -naltrexol and IS. RSD for intra-day and inter-day variations were approximately 5% and 10%, respectively for both naltrexone and 6- $\beta$ -naltrexol, while LOD was 1 ng/ml for both compounds. The specificity of the method was tested by analyzing the most commonly abused drugs. The method has been used for the analyses of plasma samples from heroin addicts on naltrexone treatment used as implants (1g, duration 5-8 weeks). Naltrexone and 6- $\beta$ -naltrexol concentrations varied from 1-7 ng/ml and 3-50 ng/ml, independent of the number o days after the last implant.

\*A.F. Davidson, T.A. Emm and H.J. Pieniaszek, *J. Pharm. & Biom. Anal.* 14 (1996) 1717.

Keywords: Naltrexone, metabolite, HPLC, heroin addicts, naltrexone implant treatment.

[Return to top](#)

© 1996 - 2008 Pellet Technologies. All Rights Reserved. | [Download as Adobe PDF](#) | [Sitemap](#)



<a href="#">Home</a>	<a href="#">Products</a>	<a href="#">Patents</a>	<a href="#">Getting Pellets</a>	<a href="#">Contact Us</a>	<a href="#">History</a>	<a href="#">Legal Issues</a>
<a href="#">FDA Notes</a>	<a href="#">FDA Package</a>	<a href="#">NJ Board</a>	<a href="#">Liver Toxicity</a>	<a href="#">Compounding</a>		

## FDA Notes

Pre-IND

June 11, 1999

Lance L. Goberman, M.D.  
One South Centre Street, Suite 301  
Merchantville, New Jersey 08109

Dear Dr. Goberman:

Please refer to the pre-IND meeting between representatives of your firm and FDA on May 26, 1999. The purpose of the meeting was to further explore the toxicological and clinical study requirements for marketing approval of your product, depo-naltrexone to block the pharmacological effects of exogenously administered opioids.

As requested, a copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, please contact Tony Chite, P.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody

Chief, Project Management Staff  
Division of Anesthetic, Critical Care and  
Addiction Drug Products, HFD-170  
Office of Drug Evaluation H  
Center for Drug Evaluation and Research

Enclosure

Pre-IND Meeting

Page 2

### Introduction:

Mr. Sasinowski began the presentation stating that Dr. Goberman and his colleagues have taken into consideration the comments provided by the division in our letter, and have decided to abandon the

pharmacokinetics-based development strategy. Instead, they plan to conduct an efficacy study and a safety study, with the help of Dr. O'Brien. Dr. DiGregorio will help address the pharm/tox issues raised in the letter. Dr. Gooberman is aware that current law allows him to compound this product for his own patients, but demand from his colleagues and his own conviction that the drug represents a public health benefit have lead him to pursue commercial distribution of the drug through the NDA process. He hopes, after initial studies are complete, to interest a commercial sponsor in bringing the product to market. However, at this point he is financing the development plan himself.

Mr. Sasinowski summarized the clinical experience and pilot data collected by Dr. Gooberman on his product since 1996.

Dr. O'Brien acknowledged a need for an efficacy study, saying that the relationship between blood levels of naltrexone and opiate blockade effect was tenuous, and because of the strong affinity of the drug for the  $\mu$  - receptor, the blockade may actually outlast the blood level. He described the proposed efficacy study, the primary purpose of which would be to characterize the duration of the opiate blockade produced by the pellet. Thirty recently detoxified drug-free former opiate addicts would receive the depo- naltrexone pellet and be challenged with 8 mg hydromorphone at 24 hours, 48 hours, 1 week, and then weekly until breakthrough of drug effect is noted. PK samples would be obtained at each visit. The primary measure of blockade would be pupillometry, chosen because it is objective and not subject to misrepresentation by patients. VAS measurements of high and rush would also be obtained as secondary measures. Patients would be followed as outpatients, and urine drug screen for opiates would be obtained as additional secondary measures of efficacy.

Dr. O'Brien then briefly described a proposed safety study, which would involve 300 patients, 100 of whom would receive repeated implants. Safety parameters would be blood chemistries and implantation site toxicity at baseline, 1 month and 2 months.

In the proposed preclinical study there would be full size pellet implantation for 60 days. There would be injection site monitoring. The recovery phase would be 30 days. The anticipated problems concerned the liver and the site where the pellet was implanted.

The Agency stated that the overview of that which was presented was good, but more substantial information was needed on this framework. The Agency would like to give the groundwork for what the sponsor needs to overcome. The sponsor prefers to have the perspective of what needs to be done and the cost involved, since most of the resources to fund this project are solely the sponsor's.

Pre-IND Meeting

Page 3

By discipline, the sponsor was informed of what additional information was needed.

#### **CHEMISTRY:**

The sponsor was briefed on the process and requirements for chemistry manufacturing and controls. An elementary description of the drug substance and the drug product was described. For the IND, Dr. Gooberman was told that the following would be required:

- Upon acceptance of the drug substance, a test should be done to establish the identity of the active ingredients. In this case, it was the naltrexone and the triamcinolone acetonide.
- An assay should be done on the finished drug product.
- The packaging for the drug should be described.
- The sterilization process, gamma irradiation, and the results of the U.S.P. sterility test for the fully packaged product should be provided.
- A limited amount of stability data should be provided to show that the material is unchanged for the duration of the clinical trials.
- Dr. Gooberman was told that the process description as provided in the pre-IND material was sufficient.

#### **PHARMACOLOGY:**

- A GLP bridging study will be needed.
- Protocol and details, including control group, needed for review with GLP study.
- Appropriate species would have the same ADME (metabolic profile) to humans.
- Batch numbers are required.

- Formulation used for the animal bridging study should be the same as the one to be used clinically (i.e., 1000 mg naltrexone pellet).
- Reproductive toxicology, carcinogenicity, and mutagenicity data are needed for package insert.
- Implantation site examination should include histopathology.
- Study in guinea pig model needed for hypersensitization concern.
- TK in recovery group should include several time points.

#### **PHARMACOKINETICS:**

For the initial IND submission, no new data is needed. However, the sponsor is encouraged to develop an in vitro dissolution release testing methodology for this product as soon as possible. Final dissolution release specifications will be set, based on dissolution release data obtained from the batch used in the pharmacokinetic study.

Pre-IND Meeting

Page 4

#### **CLINICAL:**

- The pharmacologic effect of long-term blockade of exogenous opioids is not viewed as a clinically meaningful claim. It may be acceptable to view demonstration of this effect as a surrogate, suitable for initial approval and requiring Phase IV validation in clinical trials.
- It may be possible to modify the proposed efficacy study to focus on clinical endpoints. Alternatively, it may be appropriate to study the pharmacologic effect (extent and duration of opiate blockade) separately, perhaps in normal volunteers or non-treatment-seeking non-dependent opiate abusers. A separate trial of the effect of the drug on relapse to opiate use could then be designed for optimal collection of clinical endpoints.
- The clinical efficacy study should be controlled. Either a comparison to oral naltrexone or dose-controlled study would be appropriate. Dose-control designs are also attractive for identifying the minimum effective dose.
- Complete characterization of the pharmacokinetics of the drug, particularly early after administration is necessary.
- The proposed safety study should be larger and should expose at least 100 patients for longer duration (6 months to a year). ICH guidelines on the extent of exposure for a new molecular entity call for 100-1500 patients, with 300 exposed for 6 months and 100 exposed for a year. Naltrexone is not an NME, and there is information on the safety of the oral product, but this is a new formulation and exposes patients to sustained, rather than intermittent, blood levels. The AUC may be higher than the oral product even if the Cmax is lower. Therefore, although extent of exposure can be less than the ICH recommendation, 300 total patients is unlikely to be sufficient to characterize the safety.
- Triamcinolone is viewed as an active ingredient. Possible effects of chronic exposure to triamcinolone will need to be explored in the safety studies. Furthermore, the contribution of triamcinolone to the efficacy of the product will need to be established.
- Dr. Goberman was advised to consult regulations on charging for investigational medications. As a number of his patients are involved with the court system, he was also advised to consult regulations on research involving incarcerated subjects. Dr. Goberman clarified that the subjects were not actually incarcerated; however, treatment with depo-naltrexone was the option suggested by their parole officers as a means to encourage compliance and to show the judge, etc. that they were serious about "kicking" their drug habit.

Minutes Preparer: Tony Chite

Chair Concurrence: Cynthia McCormick

#### **MEMORANDUM OF MEETING MINUTES**

**Meeting Date: May 26, 1999**

**Time: 9:30 a.m. – 10:45 a.m.**

**Location: Parklawn Bldg. 3<sup>rd</sup> floor Potomac Room**

**Application:** Depo-Naltrexone

**Sponsor:** Lance Gooberman, M.D.

**Type of Meeting:** pre-IND

**Meeting Chair:** Cynthia McCormick, M.D.

**Meeting Recorder:** Tony Chite

**FDA Attendees, titles and Office/Division:**

Cynthia G. McCormick, M.D.	Division Director	HFD-170
Celia Winchell, M.D.	Team Leader/Drug Abuse	HFD-170
Jack Longmire, M.D.	Medical Reviewer/Drug Abuse	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Michael Klein, Ph.D.	CSET Team Leader	HFD-170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokineticist Reviewer	HFD-870
Tom Permutt, Ph.D.	Team Leader/Biostatistician	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Tony Chite, P.D.	Project Manger	HFD-170

**External Attendees, Titles:**

Lance Gooberman, M.D.	Sponsor
Charles P. O'Brien, M.D.,Ph.D.	Clinical Consultant
G. John DiGregorio, M.D.,Ph.D.	Preclinical Consultant
Frank J. Sasinowski, Esq.	Regulatory Consultant

Josephine H. Torrente

Consultant

### Meeting Minutes:

The sponsor's objective of this pre-IND meeting was to further explore the toxicological and clinical study requirements for marketing approval of depo-naltrexone to block the pharmacological effects of exogenously administered opioids.

---

April 22, 1999

Cynthia G. McCormick, M.D.  
Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Re: Depo-Naltrexone Meeting

Dear Dr. McCormick:

Thank you for your letter dated April 8 granting our meeting request. Our objective for this meeting is to further explore the toxicological and clinical study requirements for marketing approval of depo-naltrexone to block the pharmacological effects of exogenously administered opioids. Accordingly, enclosed please find our meeting package which reviews the clinical data currently available on this dosage form. We do not intend to address issues related to chemistry or statistics in any detail at this initial meeting.

#### Oral Naltrexone

The safety and pharmacological efficacy of naltrexone in this indication have been established in numerous published studies spanning over 20 years, and effective blood levels of naltrexone for this indication have been reported in the literature. In 1984, the agency found Trexan® , an oral dosage form naltrexone, safe and effective for blockade of the pharmacological effects of exogenously administered opiates. The clinical data relied upon for the approval of Trexan® is indicative of the administrative difficulty associated with formal studies in this patient population.

The Summary Basis of Approval for Trexan® notes the issues involved in studying "treatment efficacy," or the course of opiate dependence. It appears that no such efficacy trials were conducted for Trexan® . Instead, indications of "pharmacologic efficacy" were noted in the published literature. The safety database for Trexan® consisted of approximately 2,000 patients exposed to drug through various open-label studies.

#### Depo-Naltrexone

Depo-naltrexone can be expected to act pharmacologically in a manner similar to oral naltrexone. The current pellet formulation has been shown to provide a sustained release resulting in greater than 1 ng/ml naltrexone throughout a 60-day period. As the agency is aware, this level of naltrexone has been shown to be effective in various literature reports. Because drug levels from the sustained release naltrexone pellets are significantly lower than those obtained by oral administration, and orally administered drug is associated with minimal adverse events, it is reasonable to expect that naltrexone pellets will not present additional safety concerns. The safety of several formulations of naltrexone pellets has been demonstrated in over 3,500 patients to date (including over 1,000 patients with the current formulation) for up to seven months with repeated implantation

of pellets.

### May 1998 Guidance Document

FDA's May 1998 guidance document entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" reviews the quantity of evidence necessary to support effectiveness of drug products. In the second entitled "Extrapolation from Existing Studies," the agency notes that:

Dose-response relationships are generally continuous such that information about the effectiveness of one ... dosage form is relative to the effectiveness of other ... dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new ... dosage form is effective on the basis of pharmacokinetic data alone. *Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new ... dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial.* In this situation, pharmacokinetic (PD/PD) relationship, are used to translate the controlled trial results from one ... dosage form to a new ... dosage form. (emphasis added)

### Conclusion

While blood levels of depo-naltrexone are not expected to be equivalent to those of oral naltrexone due to the slow release pharmacokinetics of the implantable dosage form, we believe that a conclusion of pharmacological efficacy for depo-naltrexone may be arrived at without further clinical efficacy data. In this regard, we propose to carry out a pharmacokinetic study in healthy volunteers to demonstrate that effective blood levels of naltrexone are achieved. During the same study, we intend to collect safety data on the site of implantation.

We look forward to meeting with the Division on Wednesday, May 26, 9:30 a.m. at your Offices in the Parklawn Building to discuss these issues. Should you require any additional information prior to that time, please feel free to contact me.

Sincerely,

Lance Goberman, M.D.

cc: Anthony Chite (15 desk copies)  
Project Manager

---

[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[FDA Notes](#)   [FDA Package](#)   [NJ Board](#)   [Liver Toxicity](#)   [Compounding](#)

## FDA Meeting Package

### I. Introduction

Opiate dependence is a brain-related medical disorder. Despite the existence of treatment options, illicit opiate addiction remains a serious economic, health and social issue in the United States. An estimated 600,000 patients in the U.S. are dependent on opiates<sup>1</sup>, with an increasing trend in new heroin users, especially among adolescents.<sup>2</sup> Opiate dependence has been linked to increased criminal activity,<sup>1</sup> increased prevalence of transmissible viral infections, and a greater number of emergency department visits.<sup>3</sup>

Methadone and LAAM, opiate agonists used for maintenance treatment of opiate addiction,<sup>4</sup> are Class II scheduled drugs and have raised further social and political concerns. The use of naltrexone, a non-narcotic drug approved for the blockade of the pharmacological effects exogenously administered opioids, alleviates many of these issues. Naltrexone is a pure opioid antagonist that works by blocking opiate receptors,<sup>1</sup> and does not lead to either physical or psychological dependence. Oral doses are biologically available and can provide effective opiate blockade for up to three days. There is essentially no agonist activity,<sup>1</sup> and side-effects from the drug itself have been minimal.<sup>5,6,7</sup> Clinical trials with naltrexone tablets, marketed under the tradename Revia™ by Dupont Pharma, demonstrated "complete blockade of the euphoric effects-of opioids in both volunteer and addict populations.<sup>8</sup> Naltrexone effectively blocks the cognitive and behavioral effects of opioids.<sup>1</sup>

Naltrexone was discovered in the late 1960s and evaluated at some length in the 1970s.<sup>9,10</sup> It appeared to have great promise as an adjunctive therapy in the opiate detoxification process. Although some success with naltrexone has subsequently been reported with relatively "controlled" populations such as prisoners,<sup>11,12</sup> the drug has not lived up to its original promise. There appear to be two major reasons for this sub-optimal success. First, naltrexone cannot be given until a patient is fully detoxified from opiates, as naltrexone ingestion by an active user will precipitate sudden and violent withdrawal.<sup>13</sup> Second, use of oral naltrexone as an adjunct in the post-withdrawal phase requires regular dosing; an addict who misses or avoids his/her oral dose for over three days will once again be susceptible to the effects of opioids.<sup>12</sup>

As with all orally administered products, Revia's™ ability to bring about its indicated effects is dependent upon patient compliance. Unlike most other oral therapies though, Revia™ is indicated for use in patients whose lives may make compliance extraordinarily difficult and rates of relapse are high.<sup>11,14,15</sup> Product information for Revia™ notes that: "there are no data that demonstrate an unequivocally beneficial effect of Revia™ on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance."<sup>8</sup>

Early recognition of the compliance issue with oral naltrexone led to work in the development and evaluation of slow-release subcutaneous depo-naltrexone preparations,<sup>1,17,18,19</sup> but the surge of interest apparent in the 1980s has not yet led to a published study of an effective preparation being used clinically. Providing opiate addicted patients with effective doses of naltrexone in a long-acting subcutaneous (i.e., compliance-

independent) dosage form would fill a demonstrated need in this population.

## II. Depo-Naltrexone Overview

The medical literature contains reports of effective serum blood levels of naltrexone. Chiang et al have reported that patients attaining a serum plasma concentration of 1 ng/ml naltrexone are refractory to the effects of intravenous opiates.<sup>16</sup>

The early articles which described the manufacture of naltrexone-containing pellets and their biological release in both animals and human beings demonstrated 1) a promising release profile with reasonable drug levels, and 2) prolonged resistance to opiates in both human and non-human subjects after implantation was demonstrated.<sup>17,18,19,20</sup> Work with these preparations tapered off after the mid 1980s. Three reasons have been posited for this tapering: first, the system used for the preparation of pellets in those studies was protracted and extremely expensive; second, high doses of naltrexone apparently were not achieved by the methods described; and third, incomplete detoxification may have made it difficult to initiate naltrexone therapy.

Depo-naltrexone, subcutaneously implantable pellets which release naltrexone over a 30 or 60 day period, have been compounded by pharmacists to treat individual patients since 1996. To date, over 3,000 patients worldwide have received either the 30 or 60 day pellet of depo-naltrexone, which have been shown to provide a sustained release of greater than 1ng/ml naltrexone throughout the treatment period. This prolonged interval of compliance-independent exposure to effective drug levels provides an opportunity for the beneficial effects of social and psychological intervention to have a positive impact on the patient.

Pellets are implanted subcutaneously in the lower abdomen under general anesthesia during rapid opiate detoxification or under local anesthetic otherwise. An incision of approximately one centimeter is made through the dermis. A 3.5 cm tunnel is then created under the dermis such that the pellet does not lie directly below the incision line. The pellet is deposited at the distal end of the tunnel with a trochar. The incision is then closed with an absorbable suture material, Rapide (Ethicon, Somerville, NJ). After implantation, pellets can be viewed via echograph, noting longitudinal size, transverse size and echographic shadow. As the naltrexone is consumed, the pellet becomes small and loses its shadow. By the eighth week after implantation, the pellet is no longer present.

Long-acting depo-naltrexone pellets are not a solution to drug dependence. Detoxifications need to be accompanied by attempts at social support and social change such as a 12-step program. Naltrexone is not that therapeutic environment; naltrexone is an adjunctive therapy whose goal is to give patients capable of change the opportunity to change over an extended interval during which relapse into drug-taking behavior will not renew chemical dependence.

## III. Chemistry

Depo-naltrexone (60 day) is a white cylindrical pellet approximately 12.5 mm in diameter and 9.5 mm in height containing 1000 mg. In addition to naltrexone base, the final dosage form contains magnesium stearate and trimacinalone. The compounding procedure currently employed to make the pellets is described in the attachment. The pellet is irradiated for sterilization prior to implantation.

## IV. Pharmacokinetics

As an opiate antagonist, naltrexone binds to opioid receptors in the brain and competitively inhibits the actions of opioid drugs. This inhibition markedly attenuates or completely blocks opioid-induced euphoria and physical dependence.<sup>8,21</sup> The major metabolite of naltrexone, 6-beta-naltrexol, is also thought to have opiate antagonist activity. The USP provides the following pharmacokinetic data for naltrexone (and 6-beta-naltrexol):<sup>21</sup>

Absorption: rapid and almost complete

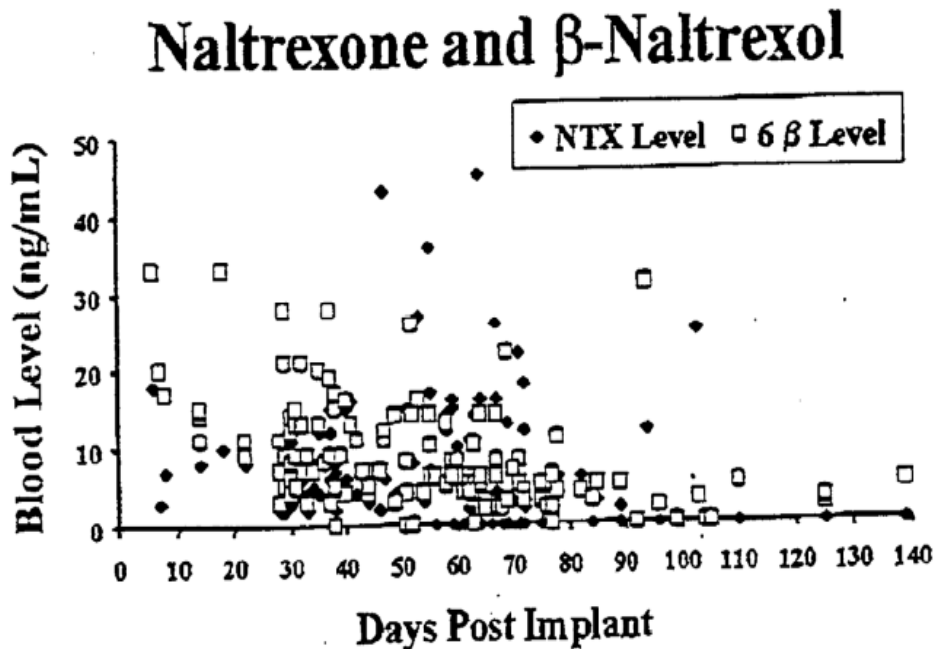
Protein binding: low (21%)

Biotransformation: hepatic; approximately 95% metabolized; subject to extensive first pass hepatic metabolism

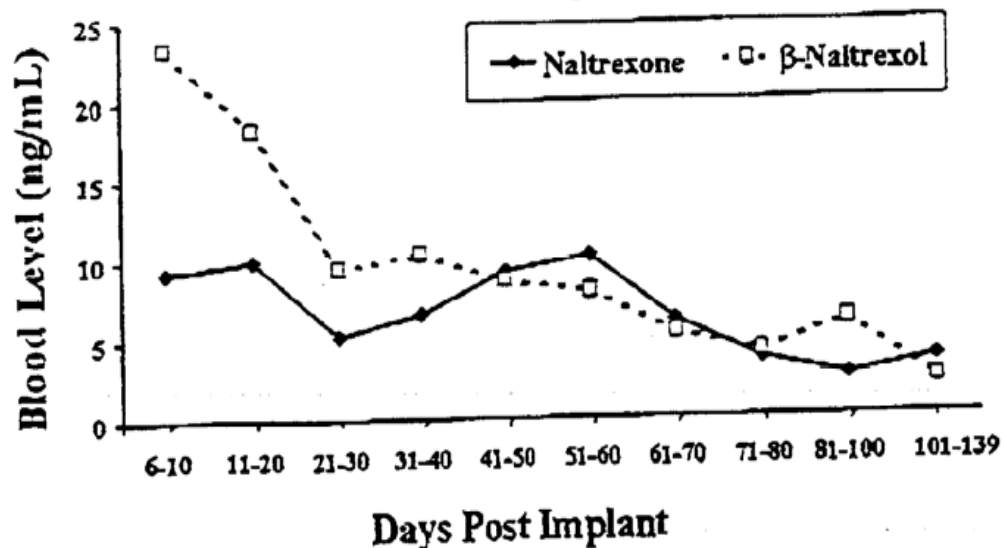
Elimination (half life):  
 naltrexone: 4 hours; independent of dose  
 6-beta-naltrexol: 13 hours; independent of dose

Elimination: primarily renal

Plasma serum concentrations of naltrexone and 6-beta-naltrexol have been obtained from 139 samples of patients receiving naltrexone pellets. The figures below demonstrate the serum concentrations of both naltrexone and 6-beta-naltrexol from six to 100 days post-implantation.



## Naltrexone and $\beta$ -Naltrexol



Naltrexone levels are initially in the range of 20 ng/ml, and level off to approximately 10 ng/ml for the remainder of the 60 day period. The metabolite, 6-beta-naltrexone remains at relatively constant concentrations between 5-10 ng/ml for the majority of the 60-day period, peaking at less than 15 ng/ml. As can be seen from this data, mean plasma naltrexone concentrations exceeded 1 ng/ml, the effective dose level for opioid antagonism<sup>10</sup>, for the entire 60-day period.

### V. Safety

Several potential problems with depo-naltrexone need to be acknowledged. First, a patient with active naltrexone blockade will not be susceptible to routine narcotic analgesia for emergent situations. Second, the effects of naltrexone on pregnancy have not been established. While one could argue that it may be safer to administer tiny doses of naltrexone via a slow-release system than to allow intermittent opiate usage during pregnancy, there is no available clinical information which one can use to evaluate risk. This clinical issue needs to be addressed. Third, the use of subcutaneous deposition does require an invasive technique, albeit minor.

While naltrexone is not associated with the development of opiate tolerance or dependence, it is important to note that detoxified patients, whether detoxification occurs through opiate blockade or some other method, must be cautioned against a return to their pre-detox opiate doses immediately after their blood levels of naltrexone return to baseline (0.0 ng/ml). Previously tolerated opiate doses could be life-threatening in patients who have lost their tolerance due to long-term blockade.

### VI. Indications of Efficacy

#### A. Oral Naltrexone

Naltrexone has been shown to be of significant benefit post-detoxification in "controlled" populations such as prisoners. Brahen et al. used the blocking effect of naltrexone to allow previously opiate-addicted prisoners, who were willing to take naltrexone, access back to the community in a work-release program.<sup>11</sup> They documented the efficacy of this program over a 10-year period. Chan, working in Singapore where all known addicts are detained by executive order, also used naltrexone in a work-release program and noted a 1-year success rate of 76.3% after initiating a naltrexone program versus a 24% 1-year success before naltrexone.<sup>12</sup> Cornish, in a study of parolees with a history of opiate abuse demonstrated 46% fewer re-incarcerations in a subset of parolees who agreed to take oral naltrexone.<sup>22</sup> Unfortunately, the clinical efficacy of naltrexone in these controlled populations has not held true for patients outside of such environments, likely due to compliance issues.

The concept of sustained-release naltrexone is not new. A sustained-release naltrexone preparation that blocks the effects of narcotics for about a month was a goal of NIDA in the 1980s and is the subject of

several publications.<sup>16,23</sup>

No adjunct in the process of treating a chronic relapsing problem should be considered a "cure." Abstinence is not an event; it is a sustained process which includes motivation, detoxification, and social/emotional interventions perhaps best achieved with a 12-step program. The goal of depo-naltrexone is narrow; to allow more time after detoxification during which other interventions might be instituted without being detailed by recurrent intoxication.

## B. Direct Opiate Challenge

A pilot study was conducted on the use of a subcutaneous depot naltrexone pellet. Fifteen patients who had received depo-naltrexone were tested with direct opiate challenge at intervals ranging from 21 to 70 (mean 41.7) days post implant. None had a response consistent with opiate effect. Depo-naltrexone may effect an extended intoxication-free interval during which efforts at lasting social and behavioral modification can be made.

The purpose of this study was to confirm that anecdotal resistance with controlled observed opiate challenge in patients with a depo-naltrexone pellet in place and to evaluate the duration of efficacy of the pellets.

### 1. Methods

All patients initially underwent rapid opiate detoxification, as previously described.<sup>24</sup> Initial pellet insertion occurred before the patient awoke from anesthesia. Some patients received subsequent pellets; in these cases, the insertion was performed under local anesthesia using 2% lidocaine with epinephrine.

All pellets used in this study contained 1000 mg of naltrexone compressed into a cylindrical form 12.5 mm in diameter and 9.5 mm high. Pellets were placed subcutaneously in the lower abdomen. An incision of approximately one centimeter was made through the dermis. A 3.5 cm tunnel was then created under the dermis such that the pellet did not lie directly below the incision line. The pellet was deposited at the distal end of the tunnel with a trochar. The incision was then closed with an absorbable suture material, Rapide (Ethicon, Somerville, NJ).

Intravenous fentanyl was used as the challenge agent. Fentanyl is a synthetic opioid with approximately 80 times the potency of morphine.<sup>25</sup> It has the shortest duration of action of the available opioid analgesics,<sup>26</sup> making it a good candidate for opiate challenge. Five cc (250 µg) of fentanyl were given intravenously for each challenge procedure. This dose is the pharmacologic equivalent of a 20 to 25 mg bolus of morphine. At this dosing, even active opiate users would be expected to have definitive physiologic responses. Patients were observed pre-challenge and post-challenge for forty-five minutes in a stable environment with no changes in lighting or any other factor which might have exogenously altered monitored parameters.

Written consent was obtained from all subjects. Separate consents were obtained for precipitated withdrawal with initial pellet insertion and for later pellet insertion in post-withdrawal patients. All participants also gave permission for the therapeutic challenges with fentanyl.

### 2. Results

Nine of the fifteen challenge subjects were men and 6 were women. The mean age of the challenge subjects was 34.5 with a range of 19 to 39. Challenges were performed as early as 21 and as late as 70 days after depo-naltrexone implantation; the mean time after implantation was 41.7 days. Fifteen challenges were performed. The results are presented in the following table.

Click to see [Responses to Fentanyl Challenge](#)

As can be seen, there were no significant changes in pupillary size or respiratory rate as measured by direct observation at 30 minutes post infusion. In patient nine, there was a subjective impression of slight pupillary change which, if present, was too slight to be reflected in a change in measured pupillary size. The most significant adverse event after fentanyl administration was what appeared to be a vasovagal response in patient five. This was short-lived and not accompanied by objective evidence of opiate intoxication.

### 3. Discussion

This pilot study suggests that depo-naltrexone effects prolonged opiate blockade, many times that achieved by oral naltrexone dosing. There was no opiate effect in 15 challenges performed a mean of 41.7 days after depo-naltrexone insertion (and as long as 70 days after insertion in one individual). This lack of response to exogenous opiate was consistent with the anecdotal reports of lack of response to street opiate usage by patients with depo-naltrexone pellets in place.

The blockade against opiate effect exhibited by the depo-naltrexone preparation is potentially crucial. Even though it cannot prevent experimentation with street drugs post-detoxification (which patients reported but which was not documented with urine testing), our evidence suggests that the depo-naltrexone did prevent those drugs from having a significant physiologic effect. Prolonged opiate blockade could prevent early re-addiction and allow a longer period for rehabilitation.

### 4. Conclusion

In summary, a challenge study of patients given a depo-naltrexone preparation has been described. The results suggest that depo-naltrexone is capable of effecting prolonged opiate blockade. The use of this pellet may be a valuable adjunct to the process of helping addicts to break the vicious cycle of opiate dependence.

#### C. Literature Report of Fentanyl Challenge

Brewer and Gastfriend<sup>27</sup> who have subcutaneously implanted 100 ng depo-naltrexone pellets into selected patients since March 1997, recently reported the results of a fentanyl challenge test performed on one patient, two weeks after receiving a second implant, to determine whether the depo-naltrexone would block opioid doses roughly equivalent to a dose of intravenous street heroin (0.25 – 0.5g).

The 30-year-old male subject underwent a 20-minute, 1000 µg intravenous fentanyl challenge while being monitored for vital signs, pupil size and oxygen saturation. The investigators reported that "No opiate effects were noted either subjectively or objectively." The subject was then given 0.4 mg intravenous naloxone and 50 mg oral naltrexone and remained asymptomatic.

#### D. Comparative Study of Abstinence Rates

A retrospective study of 655 detoxified patients was conducted to evaluate the impact of oral naltrexone versus depo-naltrexone, inserted at the time of detoxification, on self-reported 30-day abstinence rates.

##### 1. Methods

Between March, 1995 and October, 1997, 959 patients underwent rapid opiate detoxification at a private clinic in New Jersey.<sup>24</sup> The inclusion criterion was active opiate dependence. Exclusion criteria were 1) history of cardiac arrhythmia, myocardial infarction or decreased left ventricular function; 2) pregnancy; and 3) age greater than 65 years. All procedures were performed in a private outpatient setting.<sup>24</sup>

The treating physician, in the presence of a caretaker selected by the patient, explained the procedure to the patient. A detailed informed consent form was signed prior to detoxification. Oral or subcutaneous naltrexone maintenance therapy was initiated before the patient awoke from anesthesia. Physician follow-up was attempted for all patients in the 72 hours following detoxification. In many cases, there was an attempt at sustained follow-up by an office staff member. The 655 patients for whom sustained follow-up was attempted from the subjects of this report.

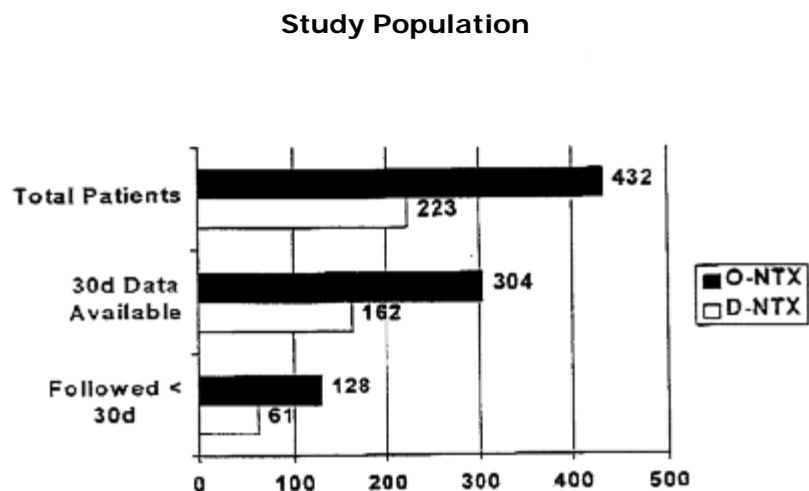
Starting in November of 1996, consent for detoxification included consent for the subcutaneous implantation of depo-naltrexone; the pellet was inserted prior to termination of anesthesia. The initial pellets totaled 600 mg with the dose later increased to 1000 mg/pellet. These two subsets are joined in the analyses described below. This change to the routine use of depo-naltrexone allows division of the population into two groups, those maintained on oral naltrexone post detoxification, the oral naltrexone group, and those receiving depo-naltrexone, the depo-naltrexone group. The two groups were compared with respect to self-reported opiate relapse. The baseline data were obtained at the time of detoxification. The follow-up data were obtained via sequential

telephone contact by office staff. T-testing was used for between-group comparisons, with a  $p < 0.05$  considered significant. Each group was considered in toto and then broken down in gender and by prior drug utilization pattern to determine if any subset behaved differently from the groups as a whole.

It is important to note that patients who claimed not to be using opiates regularly at day 30 may have tried opiates sporadically and abandoned them due to lack of efficacy. The distinction here is between those who had relapsed to regular usage and those who had not reverted to addictive drug-taking; patients who tried opiates but did not relapse to regular use are in the "non-user" category in this study. The study is thus designed as an outcome study looking not at the effect of naltrexone upon craving or initial behavior, but rather at the most crucial outcome, presence of absence of relapse.

## 2. Results

Sustained follow-up was not possible in all cases. Office staff achieved some prolonged follow-up (defined as more than 72 hours) for 655 out of the 959 detoxifications performed during the study period. There were 487 men and 168 women, with a mean age of 36 (range, 19-62). Of the 655 patients, 432 were treated with oral naltrexone and 223 were treated with depo-naltrexone. Similar percentages of each group were followed for at least 30 days after detoxification; 304 (70.4%) of the oral naltrexone subjects had 30-day follow-up data, and 162 (72.6%) of the depo-naltrexone patients had 30-day follow-up data. The breakdown is represented in the following figure.



The demographics of the oral naltrexone and depo-naltrexone groups are presented in the table below. There were two statistically significant differences between the two groups. First, the mean age of the oral naltrexone group was 37.1, slightly older than 34.9, the mean age of the depo-naltrexone group. Second, total duration of follow-up was longer for the oral naltrexone group. Average follow-up for oral naltrexone group was 97.4 days, with a range of 1 to 780 days. Average follow-up for the depo-naltrexone group 74.3 days, with a range of 1 to 412 days. Opiate or combination of opiates used prior to detoxification and the amount of opiate used were not found to be different for the oral naltrexone and depo-naltrexone groups. Breaking each group down by gender failed to reveal any difference between groups not evident in the whole-group comparisons.

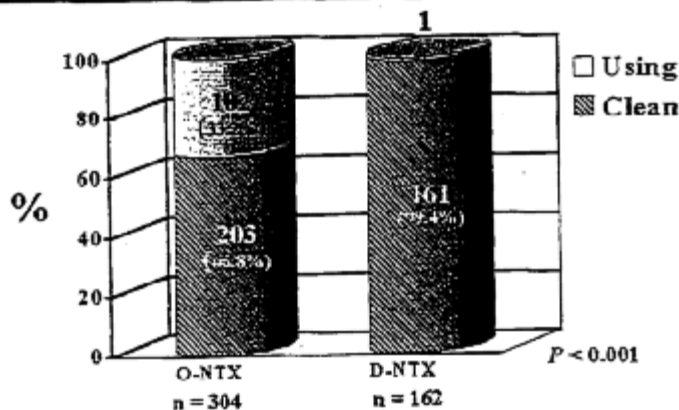
### Patient Demographics

	oral naltrexone	depo-naltrexone	p
Total Patients Studied	432	223	
Men, n (%)	324 (75.0%)	163 (73.1%)	NS
Women, n (%)	108 (25.0%)	60 (26.9%)	NS
Mean Age ± SD (range)	37.1±8.5 (19-62)	34.9±9 (19-59)	> .05
Mean Duration of Follow-Up (range)	97 (1-780)	74 (1-412)	> .05
Exclusive Heroin Users, n (%)	273 (63.2%)	148 (66.4%)	NS
Heroin, bags (range)	10.2 ± 10.3 (1-100)	8.8 ± 7.5 (1-60)	NS
Exclusive Methadone Users, n (%)	37 (8.6%)	18 (8.1%)	NS
Methadone, mg (range)	77 ± 52 (8-300)	75 ± 63 (15-270)	NS
Combo Heroin + Methadone Users, n (%)	109 (25.2%)	38 (17.0%)	NS
Heroin, bags (range)	9.2±12.1 (1-100)	7.6±7 (1-40)	NS
Methadone, mg (range)	56±60 (1-400)	54±33 (1-100)	NS
Other Opiate Combinations, n (%)	13 (3.0%)	19 (8.5%)	NS

OPIATE CHOICE BY GENDER			
Male Exclusive Heroin Users, n (%)	209 (48.4%)	109 (48.9%)	NS
Female Exclusive Heroin Users, n (%)	64 (14.8%)	39 (17.5%)	NS
Male Exclusive Methadone Users, n (%)	25 (5.8%)	13 (5.8%)	NS
Female Exclusive Methadone Users, n (%)	12 (2.8%)	5 (2.2%)	NS
Male Heroin + Methadone Users, n (%)	80 (18.5%)	29 (13.0%)	NS
Female Heroin + Methadone Users, n (%)	29 (6.7%)	9 (4.0%)	NS
Male Other Opiate Combinations, n (%)	10 (2.3%)	12 (5.2%)	NS
Female Other Opiate Combinations, n (%)	3 (0.7%)	7 (3.1%)	NS

The 30-day reported relapse results for the two populations were significantly different. Of the 304 patients in the oral naltrexone group for whom 30-day follow-up was available, 66.8% (203) stated that they were not using opiates, while 33.2% (101) admitted relapse to regular opiate usage. For 162 patients in the depo-naltrexone group for whom 30-day follow-up was available, 99.4% (161) stated that they were not using opiates, while one patient (0.6%) admitted to relapse. The difference is highly significant (p <0.0001).

### Reported Opiate Use at 30 Days



Since a significant number of patients in both populations was not successfully followed for 30 days (128,

or 29%, of oral naltrexone population and 61, or 27% of the depo-naltrexone population), one could argue that they could not be contacted because they had relapsed. Although this assumption is biased against the efficacy of depo-naltrexone, the numbers given the assumption that every patient not contacted had relapsed to regular opiate usage would be as follows: a relapse rate of 53% in the oral naltrexone group versus 18% in the depo-naltrexone group. This difference would still be significant, with a  $p < 0.001$ .

There were no significant differences in reported non-usage and relapse rates within populations for men versus women. For men in the oral naltrexone group, the relapse rate was 33.8% versus 0.8% for men in the depo-naltrexone group. For women in the oral naltrexone group, the relapse rate was 31.8% versus 0% for women in the depo-naltrexone group. Thus same-gender results within groups were not statistically different, while same-gender results between groups remained significant ( $p < 0.001$ ). Likewise, gender-based statistics given the assumption that all patients not followed for at least 30 days had gone back to regular opiate usage remained significant for between-group comparisons.

When the population is broken down by choice of opiates, relapse rates remained significantly greater for all oral naltrexone groups for which numbers were large enough to allow valid statistical analysis. For those using exclusively heroin, the relapse rate was 31.8% for the oral naltrexone population versus 1.0% for the depo-naltrexone population ( $p < 0.0001$ ). For the combination of heroin plus methadone, the relapse rate was 39.3% for the oral naltrexone population and 0.0% for the depo-naltrexone population ( $p < 0.0001$ ). There were not enough patients to demonstrate a significant difference using the same tests of statistical significance in the exclusive methadone users or the users of "other opiate combinations." (The exclusive methadone results are 26.4% ( $n=19$ ) for oral naltrexone, and 0.0% ( $n=18$ ) for the depo-naltrexone populations. The exclusive "other opiates" results were 22.3% ( $n=9$ ) for the oral naltrexone, and 0.0% ( $n=7$ ) for the depo-naltrexone population.)

### 3. Discussion

This study documents reported 30-day relapse rates after detoxification for patients receiving oral naltrexone maintenance (the oral naltrexone group) and patients receiving subcutaneous depo-naltrexone (the depo-naltrexone group). The results were statistically very significant in favor of depo-naltrexone. They remained significant even when all patients lost to sustained follow-up were assumed to have resumed active opiate usage, an assumption which would severely bias results against any such significance.

The weaknesses of the study are obvious; 1) the study was retrospective, 2) only 68% of the patients detoxified over the study interval were included in the study, and 3) the results were obtained by telephone follow-up. Yet the groups in the oral naltrexone and depo-naltrexone groups were remarkably similar, both groups were approached similarly with no evident reason why one population would lie more than the other about active opiate usage, and the statistical significance. This is evidenced by the results given the assumption that all patients not followed for 30 days had resumed opiate usage. In reality, one major reason for loss of follow-up was limitations in office staff, not a documented inability to reach patients.

The only statistical difference between the oral naltrexone and depo-naltrexone groups was a decreased mean age for the depo-naltrexone group, 34.9% versus 37.1 for the oral naltrexone group. Because early patients received oral naltrexone and later patients received depo-naltrexone, the implication is that the mean age of opiate users is decreasing. There is no obvious way in which this age difference could have biased the results.

One patient, the single patient in the depo-naltrexone group who reported resumption of opiate usage, was studied further, as he reported getting high on opiates whereas prior work with depo-naltrexone had suggested that this should not be possible. (Bartter and Goberman, submitted for publication.) He asked for repeat detoxification and agreed to come to the office for testing. After giving consent, he was challenged twice. First, he was given a challenge of 250 mcg of intravenous fentanyl (morphine equivalent, approximately 20 mg).<sup>13</sup> There were no pupillary changes, respiratory changes, or mental status changes. He was then given an intravenous challenge of 4 mg of naloxone. There were no signs of withdrawal. The interesting implication is that the patient had remained fully blocked by his depo-naltrexone pellet and that his reported highs from heroin did not represent a physiologic response.

### VII. Conclusion

Current experience with depo-naltrexone provides preliminary evidence that the pellets are easy to administer, provide a relatively consistent release of drug for 60 days, biodegrade as drug is released and have demonstrated an absence of adverse tissue reactions – all criteria which have been listed by the National Institute for Drug abuse as ideal for a naltrexone sustained release system.<sup>28</sup>

1. Effective medical treatment of opiate addiction, JAMA 1998.
2. 1996 National Household Survey on Drug Abuse.
3. 1996 Drug Abuse Warning Network.
4. Methadone label, 1998 Physicians' Desk Reference
5. Cornish JW, Jenson D, Levine S, et al. Naltrexone maintenance; effect on morphine sensitivity in normal volunteers. Am J Addictions 1993; 2:34-38.
6. Renault PF. Treatment of heroin-dependent persons with antagonists; current status. In Willett RE, Barnett G, eds. Narcotic Antagonists; Naltrexone Pharmacology and Sustained-Release Preparations, NIDA research monograph 28, DHHS publication no. 81-902, Washington, D.C., 1980:11-22.
7. Brahen LS, Capone T, Capone D. Naltrexone: lack of effect on hepatic enzymes. J Clin Pharmacol 1988; 28: 64-70.
8. Revia™ label, 1998 Physicians' Desk Reference.
9. Martin WH, Jasinski DR, Masky PA. Naltrexone, an antagonist for the treatment of heroin dependence Arch Gen Psych 1973; 28:784-791.
10. Verebey K, Volavka J, Mule SJ, et al. Naltrexone: disposition, metabolism, and effects after acute and chronic dosing. Clin Pharm and therapeutics 1976; 20:318-327.
11. Brahen LS, Brewer C. Naltrexone in the criminal justice system. In Brewer C, Ed. Treatment Options in Addiction; Medical Management of Alcohol and Opiate Abuse, Gaskell, London 1993; 46-53.
12. Chan KY. The Singapore naltrexone community-based project for heroin addicts compares with drugfree community-based program: the first cohort. J Clin Forensic Med 1996; 3:87-92.
13. Tornabene VW. Narcotic withdrawal syndrome caused by naltrexone. Ann Intern Med 1974; 81:785-787.
14. Kleber, HD, Kostan TR. Naltrexone induction: Psychologic and pharmacologic strategies. J. Clin Psychiatry 1984; 45(9): 29-38.
15. Greenstein RA, Arndt JC, McClellan DT et al. Naltrexone: A short term treatment for opiate dependence. American Journal of drug and Alcohol Abuse 1981; 8:291-300.
16. Chiang CN, Hollister LE, Kishimoto A. et al. Kinetics of a naltrexone sustained-release preparation. Clin Pharmacol Ther 1984; 36:704-708.
17. Harrigan SE, Downs DA. Pharmacological evaluation of narcotic antagonist delivery systems in Rhesus monkeys. In Willett RE, Barnett G; eds. Narcotic Antagonists: Naltrexone Pharmacology and Sustained-Release Preparations, NIDA research monograph 28, DHHS publication no. 81-902, Washington, D.C., 1980:77-92.
18. Reuning RH, Liao SHT, Staubus AE, et al Pharmacokinetic quantitation of naltrexone controlled release from a copolymer delivery system. J Pharmacokin Biopharm 1983; 11:369-387.
19. Yamaguchi K, Anderson JM. Biocompatibility studies of naltrexone sustained release formulations. J Controlled Release 1992; 19:299-314.
20. Chiang CN, Hollister LE, Gillespie HK, et al. Clinical evaluation of a naltrexone sustained-release preparation. Drug Alcohol Dependence 1985; 16:1-8.

21. Naltrexone monograph. United States Pharmacopeia.
22. Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, and O'Brien CP. Naltrexone pharmacotherapy for opioid dependent federal probationers. *J Substance Abuse Treatment* 1997; 14-529-534.
23. Sharon AC, Wise DL. Development of drug delivery systems for use in treatment of narcotic addiction. In Willett RE, Barnett G, eds. *Narcotic antagonists: Naltrexone Pharmacology and Sustained-Released Preparations*, NIDA research monograph 28, DHHS publication no. 81-902, Washington, D.C., 1980: 194-213.
24. Bartter T, Gooberman LG. Rapid Opiate Detoxification. *Am J Drug Alcohol Abuse* 1996; 22-489-495.
25. Hardman JG, Goodman AG, Limbird LE. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 9<sup>th</sup> ed. New York: McGraw Hill: 543.
26. Hardman, JG, Goodman AG, Limbird LE. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 9<sup>th</sup> ed. New York: McGraw Hill: 543.
27. Brewer C, Gastfriend DR. Letter to the Editor. *JAMA* 1998, 279:1872
28. Olsen JL, Kinel FA. A review of parenteral sustained release naltrexone systems. In Willett, RE, Barnett, G. eds. *Narcotic Antagonists: Naltrexone Pharmacology and Sustained Release Preparations*, NIDA research monograph 28. DHHS publication no. 81-102. Washington, D.C., 1981: 187-193.

[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[FDA Notes](#)   [FDA Package](#)   [NJ Board](#)   [Liver Toxicity](#)   [Compounding](#)

## Statement to the N.J.Board of Medical Examiners

Statement  
of  
Jeffrey N. Gibbs, Esq.  
Hyman, Phelps & McNamara, P.C.  
Washington, D.C.  
Regulatory Counsel to Lance Gooberman, M.D.  
Before The  
New Jersey State Board of Medical Examiners  
Special Committee Investigatory Hearing  
January 17, 2000

This statement is provided on behalf of Dr. Lance Gooberman, M.D. It describes the legal and regulatory status of the practice of pharmacy compounding: It is offered to demonstrate that the practice of pharmacy compounding is legal under both federal law and New Jersey state law, that the regulatory requirements for ensuring the safety and effectiveness of compounded drugs differ significantly from the requirements for manufactured drug products, and that Dr. Gooberman's practice of compounding naltrexone pellets for subcutaneous implantation in patients undergoing opiate detoxification is consistent with those requirements.

### Introduction

Compounding is an integral part of the practice of pharmacy. It is legal in all fifty states. Tens of thousands of compounded dosage forms are dispensed each day in the United States.

In New Jersey, compounding is defined as "the act of preparing pharmaceutical components into medications, pursuant to an authorized prescriber's medication order, including, but not limited to prescription compounding, and intravenous admixture preparation." Like other states, New Jersey state law imposes specific requirements on the practice of compounding. For example, specific New Jersey statutes require compounded prescriptions to be filled in the amount and with the drugs as prescribed by the practitioner, limit who may compound drugs and under what conditions, and establish training, documentation, and handling and delivery requirements for compounded prescriptions.

However, nothing in New Jersey law says that a pharmacist must have a specified amount of data before compounding a drug, or that a physician must have a specified amount of data before prescribing a compounded drug. And, in fact, requiring a specified amount of data in advance is entirely incompatible with compounding. Physicians often prescribe a compounded drug to meet the unique needs of a single patient. Obviously, there can be no prior clinical experience in that situation.

The practice of pharmacy compounding is distinctly different from the process of drug manufacturing. The U.S. Pharmacopoeia (USP), an authoritative reference for establishing drug standards, describes the characteristics that differentiate compounding from manufacturing. They include: "the existence of specific practitioner – pharmacist-patient relationships; the quantity of medication prepared in anticipation of receiving a prescription or a prescription order; and the conditions of sale, which are limited to specific prescription orders."

The USP has established a monograph that describes the standards for pharmacy compounding. USP took this action in express recognition of the importance of compounding. Significantly, although USP sets out detailed standards for compounding, it does not require that there be test data before a drug is compounded.

Similarly, the National Association of Boards of Pharmacy (NABP), to which most state boards of pharmacies belong, has created detailed standards for drug compounding. NABP's standards have been widely adopted by the states. However, the NABP's standards do not require that a pharmacist or physician possess any clinical data before compounding

Compounding is most frequently necessary when the patient requires a drug that is not available commercially. Because approval of a new drug application is a time consuming and expensive process, manufacturers generally only develop drugs in the strengths and dosage forms that are most likely to ensure a return on their investment. If a particular patient needs a drug in a different strength or dosage form, compounding is the means by which the physician can provide the drug to that patient. Compounding is also useful for medications that are not stable and which must be prepared in small quantities, or when the patient is allergic to something (e.g., a dye) in the commercially available form of the drug.

In 1938, Congress passed the first statute regulating the distribution of drugs. As subsequently amended, federal law requires that before the drug may be marketed, the drug company must demonstrate that the drug is safe and effective for its intended use. As a result, drug companies must undertake one or more clinical studies of sufficient size to demonstrate the safety and effectiveness of the product. By contrast, a compounded drug is not intended for general use. Thus, the regulatory scheme for ensuring the safety and effectiveness of compounded drugs is necessarily different than that for manufactured drug products.

In 1997, Congress established the regulatory scheme that now governs the practice of pharmacy compounding. The strategies selected by Congress to ensure the safety and effectiveness of compounded drugs clearly reflect the characteristic differences between compounded and manufactured drug products. The federal regulatory scheme focuses on controlling the process of compounding. It does not require a statistically significant assessment of the safety and effectiveness of the final drug product, as that assessment would be irrelevant to the needs of the patient for whom the compounded prescription was prescribed.

#### Pharmacy Compounding The Federal Regulatory Requirements

Prior to 1997, the Food and Drug Administration (FDA) had taken the position that pharmacies that compounded were subject to the new drug approval (NDA) and good manufacturing practice (GMP) requirements of the Federal Food, Drug and Cosmetic Act (FDC Act). According to the FDA, every time a pharmacy compounded a drug, it needed to comply with the GMP and NDA provisions of the FDC Act. While FDA said that in the exercise of its enforcement discretion it would normally not require pharmacies to comply with the GMP and NDA requirements, the agency also said that it had the power to compel compliance. Under those standards, compounded drugs were - in theory - subject to the same standards for safety and efficacy as drugs manufactured for use in the general population. Congress disagreed with that approach.

In 1997, Congress amended the FDC Act by adding Section 503A which governs the practice of pharmacy compounding. Section 503A exempts compounded drugs from the new drug approval and good manufacturing practice requirements of the FDC Act, provided that the drugs are compounded in accordance with specified criteria. [KDM: Quote legislative history re importance of compounding.]

These criteria include limiting compounding to licensed pharmacists and physicians, and restricting the type

and quality of the materials that may be used. It is through adherence to these criteria that the safety and efficacy of compounded drug products is achieved. Therefore, a pharmacist who compounds a drug in accordance with these criteria is exempt from the NDA, GMP and labeling provisions that govern the development of drug products manufactured for use in a broader population of patients. Thus, there are no requirements for evaluating the safety or efficacy of the final compounded drug in animal or human trials. The statute does not require test data even if a compounded drug is widely prescribed and dispensed to thousands of patients.

In enacting the pharmacy legislation, Congress was well aware of the fact that new drugs generally required controlled clinical trials. Nevertheless, Congress exempted compounded drugs from the need to meet this standard. Congress recognized that compounding, by its very nature, should not have to meet the safety and efficacy standards that apply to manufactured drugs.

#### Compounding of Depo-Naltrexone Pellets

Dr. Goberman's practice of compounding depo-naltrexone in pellet form for subcutaneous implantation in patients undergoing opiate detoxification is consistent with the criteria established by Congress for pharmacy compounding in Section 503A. Section 503A provides that compounding may only be performed by a licensed pharmacist or licensed physician subject to receipt of a valid prescription for an identified patient. Dr. Goberman complies with this requirement because he, as a licensed physician, prescribes compounded depo-naltrexone in pellet form for subcutaneous implantation in individually identified patients.

Section 503A also places limits on the type of drugs that may be used in compounding. According to Section 503A(b), a licensed pharmacist may compound a drug product using bulk drug substances that comply with the applicable USP or National Formulary (NF) monograph, when a monograph exists, as well as the USP chapter on pharmacy compounding. Naltrexone is covered by a USP monograph

Any drug withdrawn from the market because it was found to be unsafe or not effective, or any drug which presents "demonstrable difficulties" for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product, may not be used in compounding. Naltrexone is an FDA approved drug that has not been withdrawn from the market for reasons concerning its safety or effectiveness, nor has it been

identified by FDA as a drug which presents "demonstrable difficulties" for compounding. Therefore, it meets these criteria.

Section 503A also places limits on the quantity of drug that may be compounded. This includes a prohibition on "regular" compounding, or compounding in "inordinate" amounts, of drug products which are essentially copies of commercially available drugs.

Naltrexone is not commercially available in the pellet form prescribed by Dr. Goberman. Orally administered forms of the drug are commercially available and are currently used as adjunctive therapy during the detoxification process for the purpose of blocking the pharmacological effects of exogenously administered opioids. The utility of orally administered naltrexone is limited, however, as dosing is dependent upon patient compliance. Because the drug is prescribed for patients whose lives may make compliance extraordinarily difficult, the rate of relapse is high. Depo-naltrexone in the pellet form is considered significantly different from oral naltrexone. Thus, compounding of the drug in this form is not considered compounding of a drug that is otherwise commercially available, and this limitation therefore does not apply to the pellets compounded by Dr. Goberman.

While compounding may be limited to a single formulation for a single patient, that is not necessarily the case. Under Section 503A, a pharmacist can compound larger quantities of a drug, such as depo-naltrexone, for multiple patients and still not need FDA approval. Accordingly, Dr. Goberman's prescription of depo-naltrexone for multiple patients is not inconsistent with Section 503A.

The law also intends there to be limits on the quantity of compounded drugs that may be shipped across state lines by individual pharmacists or pharmacies. Specifically, Section 503A seeks to limit the interstate distribution of "inordinate amounts" of compounded drugs. The definition of what is considered an "inordinate amount" in this context is to be established by FDA with each state through a Memorandum of Understanding (MOU). FDA has said that it will not enforce this provision until an MOU is adopted. FDA has not yet adopted an MOU.

Thus, Dr. Goberman's prescriptions for compounded depo-naltrexone comply with FDA's requirements. He therefore does not need to have clinical data to prescribe this compounded medication.

#### Dr. Goberman's New Drug Application

On May 26, 1999, Dr. Goberman met with staff from the Division of Anesthetic, Critical Care and Addiction Products at the FDA. The purpose of this meeting was to explore the toxicological and clinical requirements necessary to obtain marketing approval for the use of depo-naltrexone in pellet form for subcutaneous implantation in patients undergoing opiate detoxification. In that meeting, Dr. Cynthia McCormick, the Chief of the Division of Anesthetic, Critical Care and Addiction Products, referred to the enactment of Section 503A in 1997. She specifically advised Dr. Goberman that current law allows him to prescribe compounded product for his own patients and that approval of an NDA is required only for commercial marketing of a drug. Thus, Dr. Goberman's decision to pursue FDA approval was entirely voluntary. Nonetheless, Dr. Goberman has initiated the process for clinical evaluation of the naltrexone pellets for the purpose of seeking a NDA for this indication.

FDA advised Dr. Goberman that he should conduct some animal studies to support his marketing application. This is a standard requirement for NDAs, and does not indicate that FDA believes animal testing was necessary before prescribing compounded naltrexone. Dr. Goberman has retained an expert to help him prepare the protocols for these animal tests.

During the meeting, FDA also asked that Dr. Goberman use a GMT-compliant manufacturing facility to make the naltrexone for the animal studies. Dr. Goberman has identified two potential manufacturers. He has been in negotiations with them to reach an agreement under which they would supply the materials for these preclinical tests. It must be emphasized that Dr. Goberman is now undertaking these steps - preclinical testing and reaching an agreement with a supplier of preclinical trial materials - solely to support the FDA approval process. They are not necessary to compound under the FDC Act or New Jersey law.

Dr. Goberman has begun pursuing an NDA based on the interest of colleagues and his own conviction that the drug represents a public health benefit. The NDA process is time-consuming and expensive. While he hopes to interest a commercial partner in bringing the product to market, the initiation of this process demonstrates an extraordinary personal and financial commitment to expand the availability of this medication on the part of Dr. Goberman, one that goes far beyond what physicians customarily do.

#### Conclusion

In conclusion, pharmacy compounding is legal under both federal and New Jersey State law. Federal law provides that compounded drugs are exempt for the NDA, GMT and certain labeling requirements if they are compounded for individually identified patients in accordance with specific criteria that are designed to ensure the safety and effectiveness of compounded drugs. A drug compounded in accordance with those

restrictions is exempt from the NDA, GMP, and labeling requirements that govern drug manufacturers, and does not need to be supported by clinical data.

Dr. Goberman's practice of prescribing compounded depo-naltrexone in pellet form for use in individual patients for opiate detoxification is consistent with the safety and efficacy criteria established by Congress for compounded medications. Therefore, he is exempt from any obligation under federal law to conduct clinical trials to further assess the safety and efficacy of the compounded drug. His voluntary efforts to seek NDA approval for the drug demonstrates his commitment to ensuring that the drug is made available to a broader population of patients, and his willingness to meet a more demanding standard.

Compounding is likely to grow in clinical importance in the near future. Dr. Lloyd Allen, a leading, professor of compounding and a member of FDA's Committee, recently wrote:

Requiring that physicians possess clinical data before compounding would mean that residents of New Jersey would be deprived of the significant medical benefits offered by pharmacy compounding.

[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)  
[FDA Notes](#)   [FDA Package](#)   [NJ Board](#)   [Liver Toxicity](#)   [Compounding](#)

## Black Box Warning Re:Liver Toxicity

January 21, 2000

**CONFIDENTIAL – ATTORNEY - CLIENT PRIVILEGE**

Alma Saravia  
 Flaster, Greenberg, Wallenstein, Roderick, Spigel,  
 Zuckerman, Skinner & Kirchner, P.C.  
 Commerce Center  
 1810 Chapel Avenue West, Third Floor  
 Cherry Hill, New Jersey 08002-4609

Re: Naltrexone

Dear Ms. Saravia:

You have asked us to review the black box warning which appears in the Revia (naltrexone hydrochloride) package insert (PI), the data supporting that warning and the warning's current clinical relevance. Based on our review, it appears that the black box warning for Revia is based on evidence from a small trial in a population for which the drug is not labeled and in which no clinically-relevant adverse events were noted. The original studies in the within-label patients -- opiate dependent addicts -- do not support the warning. Clinical experience and literature published subsequent to Revia's approval have apparently led the addiction treatment medical community to largely consider these warnings to be unnecessary. Our analysis is provided below.

Revia is an oral tablet dosage form of naltrexone which is FDA approved for both the treatment of alcohol dependence and the effects of exogenously administered opioids. The PI for Revia notes that the black box warning is primarily based on results of a single, small (50 patient), placebo-controlled study in an off-label patient population (obesity patients) using six times the recommended dose. In that study a substantial portion of the Revia patients developed serum transaminase elevations of three to nineteen times baseline within eight weeks of beginning treatment. The clinical relevance of this data is not apparent. The patients demonstrated no clinical signs of liver malfunction, and their transaminase levels returned to or approached baseline values within weeks of discontinuing treatment.

In addition to the PI, we reviewed the FDA Medical Officer's Summary Basis of Approval (SBA) for Revia to search for any additional evidence on the hepatotoxic potential of the drug and FDA's basis for requiring the black box warning. The SBA is an internal FDA document which sets out the reviewer's analysis of the data. The SBA does include a safety review of the obesity trials, and a conclusion based on that data that, at doses four to seven times the recommended dose, Revia "has the *potential* to cause apparently reversible hepatocellular injury in a substantial proportion of patients to whom it is administered for several weeks" (emphasis added). The dose range referred to by the medical officer would be 200-350 mg per day. The Medical Officer goes on to minimize the relevance of that study to the treatment of opioid addiction and concludes, "Clinical experience using [Revia] in detoxified, formerly opioid dependent individuals at the dose recommended in the [Revia] labeling fails to provide a basis for substantive concern about [Revia's] safety."

Results of the only placebo-controlled study in detoxified opioid dependent patients do not implicate Revia as a hepatotoxin. In that study no new laboratory abnormalities developed and there were no differences detected between the placebo and naltrexone groups. In fact, in summarizing the safety evidence from studies in this population the medical officer stated that "the enumeration of treatment emergent signs, symptoms, and abnormal laboratory findings that occurred in the clinical trials of [Revia] in detoxified opioid-dependent populations did not display a sequence or pattern that implicated [Revia] treatment as the cause of the abnormalities detected." The Medical Officer specifically emphasized that "this statement applies to the occurrence of elevated serum transaminase levels."

While FDA did not clearly articulate why a black box warning was included in the Revia PI, such a warning is typically reserved for drugs with a greater quantity and quality of clinical data in the NDA indicating that the drug may be hepatotoxic. The clinical data submitted in the NDA did not show that naltrexone was hepatotoxic in the patients who would actually be administered the drug at the recommended dose.

In 1988, Brahen confirmed the lack of effect of naltrexone on hepatic enzymes of opioid dependent patients. His research involved a within-label group of patients receiving the recommended dose for a period longer than the obesity group submitted in the NDA.

benefit of admitting patients with the sole problem of elevated hepatic enzymes generally exceeds the risk." (J Clin Pharmacol, 28(1)68-70 1988 Jan.)

Moreover, according to Dr. Charles O'Brien, Professor and Chief of Psychiatry at the University of Pennsylvania Veterans Medical Center, Revia is routinely prescribed to detoxified opioid dependent patients without the subsequent liver function monitoring recommended in the black box warning. In fact, Dr. O'Brien noted that notwithstanding the fact that patients in this population often have underlying liver disease due to years of illicit drug use, Revia is routinely prescribed.

It appears from our review that the black box warning for Revia was supported by very tenuous data and has not been found warranted by subsequent research or clinical experience.



Please let us know if we can provide you with any further information.

Sincerely,

Jeffrey N. Gibbs

JNG/rag

[Return to top](#)



<a href="#">Home</a>	<a href="#">Products</a>	<a href="#">Patents</a>	<a href="#">Getting Pellets</a>	<a href="#">Contact Us</a>	<a href="#">History</a>	<a href="#">Legal Issues</a>
<a href="#">FDA Notes</a>	<a href="#">FDA Package</a>	<a href="#">NJ Board</a>	<a href="#">Liver Toxicity</a>	<a href="#">Compounding</a>		

# Supreme Court Decision Re: Compounding

## LAW OFFICES

HYMAN, PHELPS & McNAMARA, P.C.

April 30, 2002

## MEMORANDUM

**FROM:** Jeffrey N. Gibbs  
Jeffrey N. Wasserstein  
**SUBJECT:** Thompson v. Western States Medical Center

On April 29, 2002, the United States Supreme Court issued its opinion in Thompson v. Western States Medical Center, No. 01-344 (Apr. 29, 2002). The Supreme Court affirmed the decision of the United States Court of Appeals for the Ninth Circuit Striking down section 503A of the Federal Food Drug, and Cosmetic Act ("FDCA"), which was added in 1997 by the Food and Drug Administration Modernization Act ("FDAMA"). The Court held that section 503A violated the First Amendment by prohibiting compounding pharmacies from advertising their ability to compound specific products. As a result of the Court's decision, section 503A is now void.

Section 503A had been added as part of FDAMA to address growing concerns about FDA's regulation of compounding. Specifically, FDA-after over 50 years of ignoring most pharmacy compounding activities-issued a compliance policy guide regarding compounding and began taking an active enforcement stance to restrict compounding. Section 503A purported to strike a balance between compounding and large scale compounding, which FDA believed was more akin to manufacturing. Among other restrictions, section 503A prohibited compounding pharmacies from advertising what types or classes of drugs the pharmacy could compound. The plaintiffs-several large-scale compounding pharmacies that promoted specific drugs - sued FDA to prevent the agency from enforcing the advertising restrictions.

Memorandum  
April 30, 2002  
Page 2

The District Court issued an injunction, finding that the advertising restrictions violated the First Amendment. The District Court held, however, that the advertising restrictions could be severed from the rest of section 503A, thus leaving section 503A in place, except for the advertising provisions. The Ninth Circuit agreed that the advertising restrictions were unconstitutional, but struck down all of section 503A.

The Supreme Court agreed to hear the government's petition regarding the constitutional issue.<sup>1</sup> The government argued before the Court that prior to FDAMA, all compounding was illegal and violated the "new drug" provisions of the FDCA. According to the government, section 503A was a valid compromise between allowing patients access to compounded drugs and protecting the integrity of the new drug approval process.

The Supreme Court disagreed. In an opinion written by Justice Sandra Day O'Connor for five members of the Court<sup>2</sup>, the Court held that "§503A's provisions regarding advertisement and promotion amount to unconstitutional restrictions on commercial speech...." Slip Opinion at 2. Although the Court recognized that "[p]reserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important government interest," Slip Opinion at 11, the Court did not specifically adopt the government's argument that in the absence of section 503A, all compounding was illegal. Indeed, the Court recognized the long-standing history of compounding and its value in serving special medical needs. The Court also rejected the view that advertising could be banned because physicians might prescribe unnecessary medications.

---

<sup>1</sup> Neither party presented the severability issue to the Court.

<sup>2</sup> Justice Breyer, joined by the Chief Justice, Justice Stevens, and Justice Ginsberg, dissented. The dissent focused on advertisements aimed at patients, not physicians.

Memorandum  
April 30, 2002  
Page 3

The Court found that using advertising as a proxy for determining whether compounding had crossed the line into manufacturing was inappropriate. However, the Court agreed that distinguishing compounding from large-scale manufacturing was appropriate. The Court suggested that many of the factors that were part of FDA's 1992 Compliance Policy Guide could be used. Slip Opinion at 14.

The decision will not end FDA's efforts to play a regulatory role in the field of compounding. All members of the Court agreed that it would be appropriate for FDA to require large-scale drug compounding to go through the new drug approval process. At the same time, the Court clearly articulated that the "Government also has an important interest. . .in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs." Slip Opinion at 11.

Although section 503A is now gone, this regulatory void will not last indefinitely. One possibility is that FDA will seek to reinstate the substance of its compliance policy guide, either as a formal rule, or an informal guidance. It is also possible that new legislation will be sought delineating the boundaries of acceptable compounding. Based on the Court's ruling, it would not be surprising if the Compliance Policy Guide is the starting point for any such regulatory efforts. Whatever else happens, it is now clear that advertising the ability to compound specific drugs is constitutionally protected.

\* \* \*

If you have any questions about this issue, or wish to have copy of the decision, please contact Jeffrey Gibbs at (202) 737-4288 or Jeffrey Wasserstein at (202) 737-9627.

JNW/dag

[Return to top](#)



[Home](#)   [Products](#)   [Patents](#)   [Getting Pellets](#)   [Contact Us](#)   [History](#)   [Legal Issues](#)

[For Patients](#)   [Pellet Program](#)   [Eligible Patients](#)

## Pellet Program

A pure narcotic antagonist (naltrexone) is inserted under the skin of the patient. Detoxification and naltrexone maintenance therapy is not a cure for addiction. Naltrexone maintenance therapy is a crutch to be used in early recovery. The maintenance of abstinence is best achieved through participation in a 12-step recovery program. Studies have shown that the best indicator of long-term recovery is continued participation in a 12-step recovery program. The period of abstinence during which naltrexone is used leads to a loss of tolerance to the effects of opiates. **A patient utilizing naltrexone needs to be aware that when the naltrexone pellet wears off and there is a return to using the same dose of opiates that he had previously used, the patient may kill himself.**

After an area is anesthetized with 2% Lidocaine with epinephrine, it is prepared and draped in the usual manner. An incision is made with a #15 blade, approximately one-half inch in length. A pocket is created in the area adjacent to the incision by blunt dissection with blunt curved Metzenbaum scissors. A 1-gram naltrexone pellet is inserted into the pocket and the wound is closed with 2 simple interrupted sutures of #3-0 Vicryl and the wound is dressed.

Should the patient be injured after the procedure and require analgesia (pain medications), he must inform the doctor that he is on naltrexone maintenance therapy so that the proper medications may be prescribed. Because the patient may be involved in an accident or some other occurrence that renders him unable to inform the doctor that he is on the medication, it is recommended that he wear a Medic-Alert tag which advises the doctor that the patient is receiving naltrexone maintenance therapy.

The patient must be aware that following implantation of the pellet, the following symptoms might signify wound infection: Tenderness, redness, swelling and warmth at the site of the insertion of the naltrexone. If the patient notices the development of these changes, contact the physician's office so that a prescription for an antibiotic may be called in to the pharmacist.

[Return to top](#)



- Home
  - Products
  - Patents
  - Getting Pellets
  - Contact Us
  - History
  - Legal Issues
- For Patients
  - Pellet Program
  - Eligible Patients

## Eligible Patients

Naltrexone would be appropriate for any opiate addict who wants to stop using opiates but who has never managed for long or at all except in prison, or one who thinks that relying on will power or counseling alone will not work for them. Naltrexone is not a mood altering drug and is therefore not objectionable to most individuals who advocate abstinence. We advise all patients to seek counseling, particularly group therapy and most particularly active participation in 12-step recovery programs. **We can't over-emphasize the importance of living a 12-step life.** Participation in a 12-step recovery program is the single most important form of follow-up care. We believe there is no substitute for the therapeutic value of one addict helping another.

If an addict discontinues the use of naltrexone, he must start again with a 10-14 day abstinence period. There are very few side effects from naltrexone and none of them serious. It is difficult to determine whether the symptoms one experiences initially after detoxification are due to the naltrexone or remnants of the withdrawal syndrome. Such symptoms generally cease within a week or two. Taking additional naltrexone is of no consequence. **However, if you take naltrexone while you are physically addicted to heroin or other opiates, it will cause severe withdrawal symptoms within a few minutes.**

**If you stop taking naltrexone and start using heroin again, you could kill yourself if you took your usual dose of heroin right away.**

The current price of naltrexone is approximately \$4-5.00/pill. Most prescription programs cover this medication.

It is recommended that patients wear a Medic-Alert tag (bracelet or necklace) that would inform a treating physician that the patient is on naltrexone maintenance therapy in the event that the patient is not able to communicate this information. The physician would obviously need to prescribe a non-opiate medication if pain relief was required.

[Return to top](#)



- Home
- Products
- Patents
- Getting Pellets
- Contact Us
- History
- Legal Issues
- Providers
- Injection Procedure**
- License

## Naltrexone Pellet Injection Procedure

Naloxone Challenge - 1 mg IV and observe for signs of withdrawal

- Administer prophylactic antibiotic
- Wash hands with antimicrobial soap
- Apply antimicrobial handcream
- Apply non-sterile gloves

- Cleanse skin with antimicrobial wipe
- Cleanse skin with isopropyl alcohol
- Local Anesthesia

Choose a site on the posterolateral aspect of the upper arm.

Insert a 25 gauge needle at the proximate end of the site and inject 5cc of 2% Lidocaine with Epinephrine and Bicarbonate as the needle is advanced.

Apply pressure with the syringe so that the hub of the needle causes an indentation to mark the site.

- Open packet of sterile supplies
- Prepare Area with 3 sterile betadine swabs
- Apply sterile gloves
- Apply sterile drapes
- More Local Anesthesia

Approximately One half inch distal to the mark left by the hub of the previous injection, inject 5cc of 2% lidocaine with epinephrine and bicarbonate buffer in 5cc syringe with a 18g x 1 ½" needle.

Advance the needle distally anesthetizing a tract through which to insert the pellet insertion device may be inserted.

- Make ~1cm incision with sterile #15 scalpel
- Insert the entire sterile pellet insertion device and inject the pellet pellet then withdrawal the device
- Close wound with staples from a disposable stapler
- Clean wound
- Dress wound

- Apply a bandaid.
- Apply a pressure dressing by encircling the upper arm with elastic gauze.
- Dressing to be removed within 12 hours and wound left open.

Provide wound care instruction sheet to patient

**This is the simplest method for injecting the pellet which minimizes invasiveness and encourages patient acceptance.**

[Return to top](#)



- [Home](#)
- [Products](#)
- [Patents](#)
- [Getting Pellets](#)
- [Contact Us](#)
- [History](#)
- [Legal Issues](#)
- [Providers](#)
- [Injection Procedure](#)
- [License](#)

## License to Make Pellets

Licenses are now being offered to physicians as well as pharmacists to make pellets in accordance with US patent number 6,203,813.

Instructions and assistance will be offered to those who take a license. Contact our Administrative Director, Susan Tickner, at 1.856.663.4447, for more information.

Doctors, detox centers, rehabs, hospitals, etc., may obtain a license to provide pellets by contacting:

Susan Tickner  
One South Centre Street  
Suite 301  
Merchantville, New Jersey 08109  
Phone: 856-663-4447  
Fax: 856-488-6380  
Email: [info@pellettechnologies.com](mailto:info@pellettechnologies.com)