

## **Naltrexone Treatment for Post Opiate Detoxification**

Aegis Medical Systems, Inc.  
7246 Remmet Avenue  
Canoga Park, CA 91303-1531  
(818) 206-0360 x 310

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## **Goals and Objectives/Rationale**

Narcotic antagonist pharmacotherapy for opiate abuse/addiction was first proposed by Wickler and has been used for over thirty years in the form of naltrexone hydrochloride. The treatment is based on the classical behavioral concept of “extinction.” The euphoric effects of opioids which reinforce “self administration” behavior are blocked when an individual is being treated with a narcotic antagonist. The repeated lack of reinforcement and perceived “futility” of using the agonist will gradually result in the extinction of self-administering behavior. Naltrexone is categorized as a “pure” narcotic antagonist that competes with the opioid molecules at the mu opiate receptor sites. Naltrexone is an extremely effective oral narcotic antagonist that binds tightly at the receptor sites. Because of its affinity and binding capacity, naltrexone should never be administered to any individual who is currently opioid tolerant (i.e., of heroin or synthetic opioids, including methadone or LAAM). Such administration to tolerant individuals will result in almost immediate precipitated withdrawal.

Naltrexone antagonist therapy is most often associated with post-opioid detoxification treatment including, but not limited to, heroin detoxification as well as post maintenance narcotic replacement treatment. Although naltrexone has been proven to be an extremely effective treatment option for post detoxification opiate addiction, its acceptance by patients as well as the clinical community has not been overwhelming. There are several possible explanations which could account for this lack of acceptance. From the perspective of patients, naltrexone lacks any agonistic properties which might be attractive to opiate dependent individuals. That is, naltrexone produces none of the euphoria or “high” sensations associated with agonistic medications. Secondly, naltrexone is extremely effective in producing opioid blockades. Its strong affinity and binding capacity at the opiate receptor site makes it very difficult to override the naltrexone blockade using exogenous opiates. This means that individuals who are taking a maintenance dose of naltrexone would have a difficult time injecting enough exogenous opiates (i.e., heroin) to feel the euphoric effects. It should be noted, however, that individuals often challenge the naltrexone by injecting large doses of heroin to override the blockade. In some cases, this has resulted in opiate overdose and death. Therefore, it is critical that patients being prepared for naltrexone antagonist treatment be thoroughly educated on all aspects of the medication and its effects.

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Clinician resistance to utilizing naltrexone for post-opioid detoxification treatment seems to have been centered on two key issues. First is that for patients who are being treated with naltrexone antagonist therapy narcotic analgesic medications and anesthetics may not be effective should they be needed. Put simply, patients who may need to receive opiate based analgesic or anesthetics for procedures such as surgery, dental pain or other chronic or acute pain management, will need to consider options other than opiates for such situations. Should a patient who is being treated with naltrexone be anticipating some type of medical procedure which will require opiate pain management, the patient must be withdrawn from naltrexone at least 72 hours prior to administration of the opioid analgesics. For clinicians, this has sometimes been perceived as an undesirable sequelae of prescribing naltrexone. However, in virtually all types of treatment for narcotics addiction, be it agonist or antagonist, clinical risks versus benefits to treatment must always be factored in. A second and perhaps even more frequently encountered obstacle offered on the part of the clinical community impeding the utilization of naltrexone antagonist therapy centers on the need and perceived difficulty in maintaining opiate dependent individuals opiate free for a period of time, anywhere between five to ten days following last opiate use, before induction onto naltrexone. Clinicians must ensure that patients are no longer physiologically dependent on opiates prior to beginning naltrexone therapy. Administering naltrexone to opiate tolerant individuals will result in a very quick abandonment at the receptor site of opiate molecules and a replacement at these sites with naltrexone molecules. In essence, this “flushes” the opiate tolerant patient of any opiate medications at their receptor sites and precipitates moderate to severe opiate withdraw symptoms. There is, therefore, a need to ensure that individuals being assessed and prepared for naltrexone antagonist therapy remain opiate free for a period of five to ten days prior to induction onto naltrexone. For patients on LAAM, 2-4 weeks would not be considered conservative and this is a time during which patients are extremely vulnerable to relapse to illicit drug use. Managing physicians and counselors must work very carefully with potential patients during tapering and detoxification from opiates, as well as during the opiate-free pre-induction phase, offering the patient a great deal of support and reassurance and, where needed, ancillary medications to assist the patient in remaining opiate free until induction on naltrexone.

Many experienced clinicians believe that naltrexone is most useful for highly motivated, recently detoxified patients who desire total abstinence because of external pressures. One such group, which has demonstrated success with naltrexone treatment, is impaired professional (i.e., doctors, nurses, pharmacists, attorneys, etc.) Other potential target populations are individuals at the “experimenting” stage of opioid use or those in the early stages of addiction.

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### **Clinical Issues/Contraindications**

Naltrexone, even given the above issues and concerns, remains an extremely effective alternative in the treatment of chronic opiate abuse and dependence. There may be external pressures placed upon an individual patient and/or the treatment center to avoid narcotic replacement therapy when treating opiate dependent patients. Such external pressures may be imposed from any number of sources, including the criminal justice system, family and significant others as well as the patient’s own personal desire not to start agonist treatment. In such cases, naltrexone offers a useful alternative to narcotic replacement treatment modalities. Additionally, for patients who have been on narcotic replacement therapy for a period of time and have achieved their goals of treatment and wish to medically withdraw from narcotic replacement therapy, naltrexone can be a useful transitional tool between narcotic replacement treatment and total abstinence. Perhaps naltrexone’s greatest benefit is in relapse prevention. In this way, naltrexone can offer a “safety zone” and block the effect of impulsive opiate use which may lead to relapse. Naltrexone is a non-addictive medication which is fairly inert and non-reactive with most other medications, with the exception of opiates. Caution, however, should be used when combining naltrexone with other drugs having potential liver toxicity, such as acetaminophen and disulfiram. Other drugs with which naltrexone may interact include mellaril (thioridazine) and oral hypoglycemics. Individuals with acute hepatitis or liver failure are not suitable candidates for naltrexone treatment. It is recommended that clinicians perform liver function studies prior to treatment initiation with naltrexone. Caution, is suggested when considering using naltrexone with patients whose amino transferase levels are five times above normal or higher. Because total bilirubin reflects more severe and potentially more chronic liver dysfunction it is recommended that using total bilirubin to both evaluate and monitor the development of liver problems be strongly considered when prescribing naltrexone. With the administration of the currently recommended dose of 50 mg daily or an alternative dosing schedule of 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday (weekend blockade may be achieved with the use of 100 mg on Friday), hepatic toxicity is very unlikely. However, clinicians should use their judgment when assessing the risks versus benefits in administering naltrexone antagonist therapy.

### **Psychosocial Considerations**

Naltrexone, like many other pharmacological interventions for substance abuse treatment, in and of itself, served only as an adjunctive component of treatment and is insufficient to address all of the domains of an individual’s life which may have been negatively impacted by the chronic use of illicit opiates. Therefore, it is strongly recommended that a structured psychosocial component, including group and individual counseling, be a major part of the therapeutic regimen. Both primary counselors and treating physicians should become very familiar with the naltrexone patient’s global life experiences and

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include psychosocial treatment, in the form of individual as well as group counseling, when designing a treatment plan for naltrexone patients. This is particularly important during the early stages of treatment when patient anxiety is usually highest. This psychosocial component should focus specifically on post-opioid detoxification issues, including but not be limited to, relapse prevention, financial stability and employment, motivational enhancement as well as other psychosocial aspects of the patient's life. Additionally, regular and random urine testing is a strongly recommended component of the naltrexone antagonist treatment. Urine testing serves not only as a measure of compliance in the use of illicit drugs but can also be helpful as a positive motivational tool to assist the patient. Breathalyzer (random) testing is strongly recommended to help ensure that alcohol abuse does not become an issue, particularly in light of hepatic concerns.

### **Treatment/Discharge Planning**

Treatment and discharge planning are important components to successful naltrexone treatment. Goals of treatment should be clearly stated and discussions about discharge addressed throughout. Since, unlike agonists, naltrexone is non-addictive, discontinuation of medication poses few management problems. The most important point to keep clear with patients is that a minimum of 72 hours may be required between the discontinuation of naltrexone and the ability of any prescribed opiate to produce analgesia.

### **Screening Issues for Induction**

1. **Opiate free** for 5-10 days (shorter wait requires approval by the program physician), **Methadone free** for 7-10 days or **LAAM free** for 2-4 weeks.
2. Negative urine opiate drug screen on day of Narcan Challenge
3. Liver function test (LFTs) should be obtained prior to induction of patients on naltrexone. As stated earlier in the protocol, amino transferase levels greater than five times normal should be carefully evaluated and the induction onto naltrexone be weighed in terms of risk versus benefits. Total bilirubin, as stated, may be a more specific indicator of hepatic pathology and should be considered as an additional LFT.
4. **Naloxone (NARCAN) Challenge**

Narcan (naloxone hydrochloride) is an injectable, short acting, pure narcotic antagonist. Naloxone is most commonly associated with its use in emergency medicine to reverse the effects of opioid overdose, such as respiratory depression, sedation and hypotension.

For purposes of treating patients using naltrexone antagonist therapy, Narcan is utilized in helping to diagnose current opioid tolerance. In such cases, this is more commonly

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referred to as a “Narcan Challenge.” A Narcan Challenge, as described below, should usually be completed and successfully passed prior to administration of naltrexone. Exceptions to this policy might possibly include cases where an individual was known to have been in custody for a sufficient amount of time prior to starting naltrexone.

- a. Check and record pupil size and vital signs immediately before and 15 to 20 minutes after Narcan Challenge. Evaluate for other symptoms of withdrawal, including but not limited to, gastrointestinal discomfort, piloerection, rhinorrhea, diaphoresis and yawning, etc.
- b. Narcan Challenge may be administered using 0.8 mg Narcan intravenously or sub-cutaneously.

**Intravenous**

- a. Give 0.2 mg by I.V. push and observe for 60 seconds. If no pupillary dilation or signs of withdrawal, give balance of 0.6 mg.
- b. Wait 20 minutes and check for signs/symptoms of withdrawal

**Sub-cutaneous**

- a. Give 0.8 mg sub-cutaneously
- b. Wait 20 minutes and check for signs/symptoms of withdrawal
- c. Signs and Symptoms of positive Narcan Challenge
  - 1) Objective—tearing, sweating, goose bumps, shakes, vomiting, pupillary dilatation, vital sign increases
  - 2) Subjective—feeling of temperature change, joint and/or muscle pain, bone pain, nausea, abdominal cramping, skin crawling

**Positive (Failed) Narcan Challenge**

If, after administering I.V. or subcutaneous Narcan per the above protocol, the patient begins to manifest or complain of withdrawal symptoms, the Narcan Challenge should be considered “positive” (not successfully passed). **NALTREXONE SHOULD NEVER BE ADMINISTERED IN THE PRESENCE OF A POSITIVE NARCAN CHALLENGE.** Emergent (precipitated) withdrawal symptoms should be carefully monitored and evaluated by treating physician. Mild to moderate withdrawal symptoms can often be managed utilizing non-opioid medications, including clonidine, similar to those listed below. In cases of severe precipitated withdrawal, the physician may elect to administer a small amount of oral or parenteral opioids to control withdrawals.

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## **Naltrexone Dosing With Negative Narcan Challenge**

### Day 1

Upon satisfactory completion of the Narcan Challenge and with no opioid withdrawal symptoms being manifested, a patient should be dosed with 25 mg of naltrexone. Ideally, following the oral administration of 25 mg, the patient should be observed or contact made with the patient over the next six hours to assess for precipitant emergent withdrawal symptoms. Sometimes, even following Narcan Challenge, there may be residual opioid molecules residing at receptor sites which may be dislodged following the administration of oral naltrexone. Additionally, patients may be very anxious about starting naltrexone treatment. Anxiety can lead to manifestation of pseudo withdrawal as well as other symptoms, including gastrointestinal distress which may be more related to the anxiety of starting naltrexone than to actual opiate withdrawal. Wherever possible, the patient should be evaluated for up to 6 to 10 hours following naltrexone induction.

### Day 2

Prior to receiving the day 2 dosage of naltrexone, 50 mg p.o., the patient's condition should be reviewed with particular attention to withdrawal symptoms that may have been precipitated following the dosage of Day 1. Attention should be paid to how the patient slept the night before, inasmuch as sleeplessness often accompanies withdrawal as well as the anxiety of beginning a new treatment regiment. If such symptomatology occurs, it is recommended that the clinician evaluate for a short duration of ancillary medication to address these issues and proceed with naltrexone treatment. A urinalysis is recommended to determine if there are opiates present in the system.

It is not unusual for a patient to "test" the blockade effects of naltrexone during the early stages of treatment. It is useful to discuss with the patient his/her possible use of opiates after the first or second dose. Even if the patient states the opiate use occurred, a second dose of naltrexone may be administered. It may, however, be clinically prudent to administer another dose of 25 mg and observe the patient for emergent withdrawal symptoms. If none are present after 20-30 minutes, then a second 25 mg may be administered. The patient may be dispensed 50 mg per day, however, inasmuch as clinics are often not open on Saturday and Sunday, the patient may be dosed 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday. If withdrawal symptoms occur on day one or two after dosing or following heroin/opiate use the day before, these may be managed with ancillary medications (see below). Another Narcan Challenge should be administered and successfully passed prior to resuming regular naltrexone dosing.

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### **Naltrexone Dosing (if Challenge is Passed) Summary**

Day 1—25 mg p.o.

Day 2 and onward—50 mg p.o. each day

OR

Monday 100 mg p.o.

Wednesday 100 mg p.o.

Friday 150 mg p.o (warning—doses higher than 300-350 mg per week suspected of causing increased risk of hepatotoxicity)

### **Common Ancillary Medications**

For those dependent individuals requiring withdrawal symptom alleviation until Narcan Challenge can be given and successfully passed, the following medications may prove useful.

1. Clonidine 0.1 mg qid to q4h, p.o. or sublingual (mild withdrawal symptoms, e.g., runny nose, goose bumps, yawning, etc.)
2. Ibuprophen (bone/joint aches and pains)
3. Imodium (diarrhea)
4. Tigan (nausea)
5. Sinequan (sleep disturbance)
6. Trazadone 50 mg #2 hs. (sleep disturbance)
7. Vistaril (sleep disturbance)

Above medications may be given for 5-10 days before Narcan Challenge or following a positive challenge and then discontinued. These medications are to be dispensed by clinic staff at clinic on daily basis—weekend take-home only. Experienced clinicians suggest that some ancillary medications may be useful during the first few days following naltrexone administration.

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### **Steps In Beginning and Measuring Outcomes in Naltrexone Treatment**

1. Successful detoxification from heroin (using methadone, LAAM, buprenorphine)
2. Successfully maintained patient (opiate-free for 5-30 days, depending on pre-naltrexone opiate use)
3. Educate patient regarding naltrexone and the appropriate informed consent
4. Successfully passing (negative) Narcan challenge
5. Induction and maintenance on naltrexone
6. Random urine testing for:
  - a. Alcohol
  - b. Amphetamines
  - c. Barbs
  - d. Cocaine
  - e. Marijuana
  - f. Opiates
7. Record of percentage of positive/negative urine tests
8. Record of results of breathalyzer testing and tracking of co-occurring psychiatric disorders
9. Regular attendance in counseling sessions
10. ASI administered at beginning and every six months throughout treatment