

Forum

Naltrexone in the Prevention of Opioid Relapse

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ABSTRACT

Naltrexone was synthesized in 1965, and tested during the 1970s and early 80s, as a pharmacotherapy for helping eliminate drug cravings and opioid-seeking behaviors, thus preventing opioid relapse. It was approved for this purpose by the U.S. FDA in 1984; yet, naltrexone has been largely underused by addiction treatment practitioners.

Naltrexone tightly binds to opioid receptors in the brain, blocking opioid effects and reinforcement from its use. Furthermore, there is no opioidergic reinforcement of triggering cues and behaviors associated with impulsive drug use, so conditioned abstinence symptoms and craving can be reversed. *A naltrexone-maintained patient is more capable of adapting to everyday life in a world filled with drug-using reminders and high-risk situations.*

Naltrexone is administered orally once daily, or less frequently in higher doses. It is largely devoid of side effects and its effective use without serious adverse events has been clinically demonstrated in diverse patient populations during many years of study. There are several requirements for successful naltrexone therapy: 1. selecting patients with sufficient motivation to begin treatment; 2. successfully withdrawing patients from opioids, and keeping them opioid-free prior to starting naltrexone; 3. maximizing retention in treatment and compliance with taking naltrexone.

When patients are motivated to remain opioid-free and have adequate social support networks, treatment retention, medication compliance, and opioid abstinence rates increase significantly. Naltrexone also must be combined with appropriate psychosocial therapy for avoiding relapse and maintaining long-term abstinence.

New Solution for an Ancient Problem

Opium and its derivatives have been used as medicine and for pleasure in various cultures since 4000 BC. While facilitating relief of much human suffering, these drugs also fostered addiction in many users. Attempts to synthesize less problematic opioid agents have failed, as evidenced by the introduction of “nonaddictive” heroin in 1890 (Gold et al. 1982).

According to the most current data, in year 2000 there were about 1.1 million heroin users in the United States, including nearly 900,000 chronic abusers (ONDCP 2002). In 1999, only 177,000 persons entered any type of treatment for opioid injection-drug abuse and, importantly, there was an increasing trend in admissions of young people aged 15 to 25 (SAMHSA 2002).

Of particular concern, there has been a sharp increase in the illicit use of prescription semisynthetic-opioid drugs, such as oxycodone and hydrocodone, including an alarming number of deaths (NIDA 2001). Abuse of the long-acting analgesic OxyContin® has received special notice (Rosenberg 2002), and most persons addicted to this analgesic require medication-assisted treatment to over-

come their dependency (CSAT 2001).

Naltrexone was synthesized in 1965 and tested during the 1970s and early 80s as a pharmacotherapy for helping eliminate drug cravings and opioid-seeking behaviors, thus preventing opioid relapse (Ginzburg and Glass 1984). It was approved for this purpose by the U.S. FDA in 1984 (Pfohl et al. 1986).

Although naltrexone was demonstrated as a potent and effective medication, it has been underused in clinical practice (Resnick 1998). Only about 1% to 3% of opioid-addicted persons who might benefit have received naltrexone and further research on this modality has been practically at a standstill since about 1985 (Rounsaville 1995). During the 1990s, the research focus shifted to naltrexone in treating alcoholism, for which it was FDA-approved in 1994.

Pharmacologic Characteristics

Naltrexone has a number of characteristics that are of value as a pharmacological adjunct for treating opioid addiction. These are summarized in *Table 1*.

It is a nonaddicting, relatively pure mu-opioid antagonist; that

is, it displaces opioids present on opioid receptors in the brain and blocks effects of subsequent opioid administration (Kleber 1985). Naltrexone also has been successfully used as a component of opioid-detoxification procedures (Buntwall et al. 2000; Leavitt 1998b).

Metabolism is via the liver, with transformation to the active metabolite 6-beta-naltrexol. There is some individual variation in the absorption and distribution of naltrexone, and its degree and duration of opioid blockade; however, there is no significant accumulation of the drug (Gold et al. 1982).

The half-life and elimination phase of naltrexone are sufficient to permit once-daily oral dosing, or less frequently at higher doses. It may not be started in persons actively using opioids, since it precipitates immediate withdrawal symptoms with potentially serious effects (Gonzales and Brogden 1988; Judd 1997; Miotto et al. 2002), and a prior abstinence period of 5 to 7 days from most opioids, or 10 to 14 days from methadone, is necessary (Kleber 1985; Resnick 1998).

Some characteristics of naltrexone may limit its use. For example, survey results have indicated that the required opioid detoxification followed by treatment with a drug that would keep them from getting high was unacceptable to a significant percentage of patients (Rounsaville 1995). Therefore, patient selection and motivation become important factors in successful outcomes (as discussed below).

Scientific Rationale

The explanation for how and why naltrexone works is fairly straightforward. More than a half-century ago, Wikler (1948) suggested that opioid craving and continued drug use might be eliminated if certain reinforcing or motivating effects were blocked at critical points.

Euphoria stimulated by opioids is a desired, reinforcing, effect; but as it wears off the person experiences uncomfortable withdrawal (abstinence) symptoms and intense drug craving. Then, taking more opioid to relieve craving and abstinence symptoms becomes reinforcing because it helps avoid unwanted effects. This cycle often is repeated many times each day, leading to psychological as well as physical addiction (Gold et al. 1982).

Opioid craving and withdrawal also become strongly associated with environmental cues. People, places, things, and feelings once associated with drug taking can activate “conditioned abstinence” symptoms long after opioid use has stopped and physical addiction has been eradicated. These are identical to opioid withdrawal symptoms – aches, chills, nausea, etc. – which stimulate drug craving and relapse, much as a ringing bell will stimulate a trained animal to salivate (Gold et al. 1982; O’Brien et al. 1984; Resnick 1998; Valentine and Meyer 1976).

By blocking opioid receptors, naltrexone interrupts the cycle of reinforcement and addiction. It suppress effects of opioids if the person tries to get high and, at the same time, it extinguishes conditioned abstinence symptoms in response to cues associated with drug use (Gold et al. 1982; O’Brien et al. 1984; Wikler 1973).

Wikler (1973) had proposed that active extinction procedures, whereby the patient actually injects or consumes the opioid of choice

Table 1: Naltrexone Characteristics

- Once-daily or less frequent oral administration.
- Blocks the euphoric high of opioids.
- No psychotropic or reinforcing effects.
- Nonaddicting, with no withdrawal symptoms on cessation.
- No increasing tolerance to its opioid-antagonist actions.
- Absence of serious adverse reactions or toxicity, even in long-term use.
- Essentially no abuse potential.
- No “black market” resale value or potential for diversion.
- Easy availability at reasonable cost.

while blocked by naltrexone, would be most effective. This approach has only been feasible during controlled experiments in hospital settings (O’Brien et al. 1984).

In practice, many patients challenge the naltrexone blockade on their own by taking illicit opioids during outpatient treatment; however, such “lapses” with naltrexone present would not lead to relapse and, in fact, aid in the extinction process (Crabtree 1984; Renault 1980).

It also is beneficial for patients to be repeatedly exposed to environmental cues while taking naltrexone. In effect, naltrexone allows the triggering “bells” to ring for the patient without reinforcement; thereby, conditioned abstinence and craving become extinguished over time (Gold et al. 1982; Leavitt 1998a; O’Brien et al. 1984; Resnick 1998).

In sum, naltrexone’s advantage is in protecting the individual from opioid effects leading to relapse. No reinforcement of triggering cues and behaviors that motivated impulsive drug use exists, so conditioned abstinence and craving can be reversed (Crabtree 1984). A naltrexone-maintained patient becomes more capable of adapting to everyday life in a world filled with drug-using reminders and high-risk situations (Carroll 1997).

Supportive Evidence

In 1984, Crabtree commented that more than 30 studies had evaluated naltrexone in 2,000 opioid-dependent persons. Generally, those patients who stayed in treatment longer and were compliant with taking naltrexone remained opioid-free (Crabtree 1984).

In a review by Gonzales and Brogden (1988) of 13 studies between 1973 and 1984 enrolling nearly 1,200 patients, naltrexone was consistently beneficial in reducing or eliminating (extinguishing) drug craving and opioid-seeking behavior. In non-comparative trials of select patients, up to 85% of urine screens were free of illicit opioids during naltrexone therapy.

Some studies have reported more modest, but still significant, success. A clinical trial in Italy, enrolling 52 working-class patients in a naltrexone plus psychosocial therapy program, demonstrated treatment adherence and subsequent opioid-abstinence in 41% of subjects at the 6-month followup. However, only 6% of patients who did not stay on naltrexone remained opioid-free; almost a 7-fold difference (Schifano and Marra 1990).

Typically, persons facing some sort of consequences for opioid relapse have remained in naltrexone treatment and opioid-free significantly longer. The greatest response rates have been observed in highly motivated patients, such as healthcare workers or professionals at risk of losing employment or licensure, or parolees and probationers whose liberty was at risk.

For example, Cornish et al. (1997) reported that, among 51 Federal probationers and parolees with a history of opioid addiction, half of those receiving naltrexone plus drug counseling remained in treatment for 6 months versus only a third of those receiving counseling alone (controls). Naltrexone-treated subjects had less than a third as much opioid use as controls (8% vs 30%) and were half as likely to be returned to prison within 6 months.

Yeo (1997) reported a study among parolees in Singapore demonstrating that naltrexone therapy more than doubled the chances of formerly opioid-addicted persons completing a one year followup program, compared with released prisoners not receiving naltrexone. Similar success with naltrexone during a jail work-release program had been reported in the U.S. by Brahen and colleagues (1984).

Washton and colleagues (1984) reported on naltrexone therapy in 114 opioid-detoxified business persons. More than 60% completed 6 months of treatment (also including psychotherapy and counseling) without opioid relapse, and 20% discontinued naltrexone earlier but remained opioid-free in the rehabilitation program. At 12 to 18 months followup, 64% of all patients were abstinent, however, business people completing 6 months of naltrexone therapy were three times more likely to be opioid-free, employed, and continuing in treatment at followup than those who had discontinued earlier (68% vs 23%; see *Figure 1*).

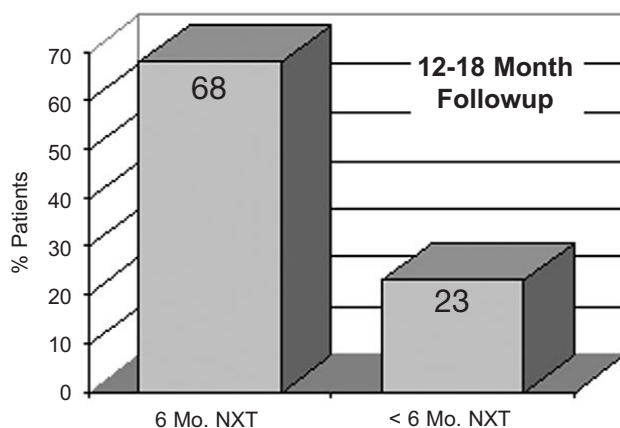


Figure 1: Percentage of patients opioid-free, employed, and continuing in treatment at 12-18 months followup (Washton et al. 1984)

This same research team (Washton et al. 1984) reported that 13 of 15 physicians (87%) who had completed a 6-month naltrexone plus psychotherapy program were opioid-abstinent at 12 to 18 months followup. Similarly, Roth and colleagues (1997) reported that 94% of 18 referred healthcare professionals (nurses, nurse-anesthetists, pharmacists) achieved long-term opioid abstinence after an average 8 months of naltrexone administration and nearly 2 years in the rehabilitation program.

In balance, there also have been noteworthy failures of naltrexone therapy in certain circumstances. All 27 patients entering a Russian naltrexone maintenance program left within 50 days (96% within about a month) and relapsed to opioid abuse (Azatian et al. 1994). Importantly, three-quarters of patients were unemployed and all had been using particularly potent and pure locally-produced opioid preparations. Furthermore, there was no psychosocial therapy component of this program, even though 89% of patients were diagnosed with personality disorders (borderline, antisocial, and paranoid disorders being dominant).

Candidates for Therapy

Based on past clinical experience and current needs, several groups of patients may especially benefit from naltrexone for opioid

Table 2: Candidates for Naltrexone Therapy

- Former opioid-addicted persons who have been drug-free – e.g., in a rehabilitation center, therapeutic community, or prison – and wishing to remain abstinent.
- Professionals – healthcare workers, lawyers, pilots, business people – facing loss of employment or licensure due to opioid abuse.
- Methadone-maintained patients who are switched to naltrexone during supervised methadone withdrawal.
- Opioid-dependent persons who prefer to try alternative pharmacotherapy prior to methadone.
- Individuals who have been drug-free but recently relapsed on opioids.
- Persons currently abstinent but concerned about possible stress-induced relapse.
- Younger persons at early stages of opioid dependence.

dependence. These are outlined in *Table 2* (Crabtree 1984; Kleber 1985; Rawlins et al. 1976; Renault 1980).

The last four groups in Table 2 represent persons not traditionally included in clinical trials. Ease of naltrexone induction in the opioid-detoxified patient and the lack of withdrawal syndrome if discontinued make naltrexone relatively easy to start and stop. This is a persuasive argument for considering a therapeutic trial of naltrexone prior to venturing into long-term methadone maintenance.

Naltrexone may be especially appealing for use as first-choice therapy in younger persons, considering the increases in prescription opioid and heroin abuse in this population (Rounsaville 1995). According to product labeling, the safe use of naltrexone in persons under age 18 has not been established (DEPADE® 2000), and the drug has variable effects on neuroendocrine function (Gonzalez and Brogden 1988; Kleber 1985). However, a number of authors have suggested its potential value in teenage opioid users (Crabtree 1984, Renault 1980, Valentine and Meyer 1976), and naltrexone has been used in children (Campbell et al. 1990) and adolescents (Lifrak et al. 1997) for disorders other than opioid addiction without any reported complications or adverse effects.

Clinical Protocols

Dosing Quantity/Frequency

The traditional advice to “start low and go slow” regarding medication dosing may be appropriate with naltrexone (Dougherty and House 2001). An average daily dose of 50 mg naltrexone typically blocks the effects of 25 mg intravenous heroin for 24 hours, and several dosing protocols have been described (Brahen et al. 1984; Gold et al. 1982; Schifano and Marra 1990; Yeo 1997).

A conservative approach entails starting with 10 mg of naltrexone (or about a quarter of a 50 mg tab) and increasing the dose by 10 mg each day until a 50 mg daily dose is achieved. The patient may be converted to a Monday-Wednesday-Friday regimen of 100-100-150 mg, respectively, and twice weekly dosing also has been mentioned as feasible (350 mg/week total). Another protocol uses 25 mg for two days, 50 mg for two days, and then the 3 times weekly protocol.

Individual variation in naltrexone metabolism has been noted, so dosing may need adjusting (Gold et al. 1982; Gonzales and Brogden 1988). Current thinking regarding naltrexone used for alcoholism is that doses of up to 150 mg/day can be safely used, and this enhances treatment retention and compliance in many patients (Volpicelli 2001).

Therapy Duration

Wikler (1973) suggested that conditioned abstinence could last for an extended period of time following the last opioid intoxication episode and he recommended a one-year course of naltrexone therapy. Others have recommended that patients stay on naltrexone for at least 6 to 12 months (Gold et al. 1982, Resnick 1998), and to discontinue it only after an extended period of opioid abstinence. A full year would make sense in allowing for an annual cycle of events – holidays, birthdays, anniversaries, etc. – that might have served as triggers for drug binges.

Kleber (1985) suggested that naltrexone therapy might range from a few months for individuals who have relapsed after long-term prior abstinence, to maintenance for years in persons with high access to opioids or histories of repeated relapses. Some patients might require multiple courses of naltrexone therapy at different stages of their opioid-using careers, including intervals of time when methadone maintenance might be most appropriate.

A lesson learned from naltrexone in the treatment of alcoholism is that the drug can be effective for “targeted” use to defend against potential relapse at times when craving or drug taking are likely (Heinala et al. 2001; Kranzler et al. 1997; Volpicelli 2001). This could be applicable for rehabilitated opioid-addicted persons who are advised to carry a tablet at all times to use prophylactically in advance of high risk or stressful situations (Leavitt 1998a, Resnick 1998).

Safety

Clinical trials have consistently concluded that naltrexone is medically safe, which prompted Gold and colleagues to assert that “the major side effect of naltrexone is the prolongation of life” (Gold et al. 1982).

Naltrexone has been associated in detoxified opioid-addicted persons with infrequently reported nausea, gastric discomfort, headaches, sleep disturbances, drowsiness, skin rashes, and decreased appetite (Gold et al. 1982; Gonzales and Brogden 1988), which usually dissipate after the first 1 to 2 weeks of treatment (Rounsaville 1995). Medication might be switched from evenings to mornings, or taken after meals, to alleviate many symptoms (Dougherty and House 2001). It has been suggested that some effects might be attributed to a mild, temporary abstinence syndrome influenced by naltrexone’s complete opioid blockade (Gonzales and Brogden 1988; Marrazzi et al. 1995).

Naltrexone undergoes first-pass metabolism in the liver via glucuronic acid conjugation, and does not interact with drugs metabolized via P450 enzyme system pathways. Therefore, it has been used effectively and safely in conjunction with numerous psychotropic agents for treating concurrent psychiatric disorders, such as anxiety or depression (Gold et al. 1982).

Some prescribers have been concerned about a possible need for frequent liver enzyme monitoring due to effects of naltrexone on liver function noted in the product literature (DEPADE® 2000; ReVia® 1997). These precautions resulted primarily from a single postmarketing study in which there were elevated liver enzymes in small groups of obese patients, age 40 and above, receiving 300 mg/day of naltrexone (Pfohl et al. 1986).

“The major side effect of naltrexone is the prolongation of life.”

In other investigations, neither elevated enzymes nor other liver damage were observed in similar patients at comparable or higher doses for up to 2 years (Croop et al. 1997; Marrazzi et al. 1995, 1997). Sax et al. (1994) reported that administration of 300 mg/day of naltrexone for up to 36 months did not significantly alter hepatic function.

Kleber (1985) has noted that, during 11 years of testing naltrexone for opioid addiction prior to FDA approval, many persons with minor liver abnormalities were treated with naltrexone without developing clinical problems or worsening of hepatic function. However, product labeling indicates that naltrexone is contraindicated in patients with acute hepatitis or liver failure.

There also have been concerns about opioid overdose in persons who discontinue naltrexone and impulsively take opioids, since there is a loss of tolerance and upregulation of opioid receptors while on naltrexone (Hardman and Limbird 1995; Miotto et al. 2002). However, Miotto and colleagues (2002) recently commented that, in cases reported to date, “there did not appear to be an association between naltrexone taking and overdose or suicide,” and detrimental effects of opioid supersensitivity induced by naltrexone have not been confirmed. Furthermore, in patients actively taking naltrexone, Kleber (1985) observed that overdose from attempting to override the opioid blockade is theoretically possible but was not a clinical problem during the extensive research on naltrexone.

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Retention/Compliance Critical

The success of a naltrexone-assisted rehabilitation program hinges on patient retention in treatment and compliance (adherence) with taking the medication (Gold et al. 1982). Naltrexone maintenance is effective *as long as the drug is taken as prescribed*. Even if impulsive opioid use occurs, it has no more effect than placebo and the patient is protected from relapse (Brewer 1996; Resnick 1998).

However, qualities of naltrexone that may hinder retention and compliance need recognition (Gold et al. 1982; Renault 1980):

- There is no direct relief of unpleasant symptoms afforded by naltrexone (a quality shared by many other medications, such as antihypertensives, which have compliance difficulties).
- Terminating naltrexone or skipping doses does not precipitate severe withdrawal, as do opioids.
- Within a day or two of stopping naltrexone, effects of opioids can be felt; thus, recidivism can be swift.

As noted above, retention and compliance have been best in motivated individuals with strong support systems. Conversely, individuals with few socioeconomic supports or incentives for rehabilitation tend to fare poorly (Resnick 1998).

Patients, as well as their support persons, need education on how naltrexone works and the critical importance of absolute compliance with the dosing regimen. It is advisable to assign a medication-monitoring person with whom the patient lives; although, in some cases an employer, parole officer, clinic nurse, or other authority figure has been used (Resnick 1998).

Periods of increased stress or physical discomfort of any kind have been identified as factors influencing treatment discontinuation (Grey et al. 1986). Medical monitoring, intensive psychosocial interventions, and naltrexone dose adjustments might be helpful during such times.

Adjunctive Psychosocial Therapy

Clinicians have typically found that merely alleviating physical dependence on opioids does not result in sustained abstinence following detoxification (Gold et al. 1982). Furthermore, patients taking naltrexone, and some healthcare practitioners, tend to wrongly view the medication as a treatment that will produce a “cure” for opioid addiction (Crabtree 1984).

Naltrexone actually creates circumstances allowing rehabilitative treatment to take place, by facilitating an opioid-free setting unencumbered by triggering cues and conditioned abstinence symptoms (Resnick 1998). Adjunctive psychiatric evaluations, counseling, family therapy, participation in 12-step groups, and other psychosocial interventions are vitally important (Leavitt 1998a), and these must be tailored to individual patient needs (Ginzburg and Glass 1984; Kleber 1985).

Therapy involving families and/or “significant others” has been repeatedly recommended as beneficial (Brewer 1996; Crabtree 1984; Galanter 1993; Kleber 1985; Rounsaville 1995), partially because these persons serve as “coercive agents” fostering treatment retention and compliance (Kleber 1985). Naltrexone combined with behavioral and family therapy has improved long-term retention in treatment more than four-fold compared with patients receiving naltrexone alone (Gonzales and Brogden 1988).

Pragmatic Perspective

Investigations of naltrexone for opioid addiction have not assessed the efficacy of specific psychotherapeutic modalities. However, clinical trials of the drug for alcoholism found that therapy centered primarily on drug-abstinence was much less effective than coping skills training that helped patients identify triggers and avoid relapse. With this latter approach, naltrexone-treated patients still tended to sample alcohol at some point, but they significantly decreased the extent of drinking and rate of progression to full relapse. Those who drank also experienced significant reductions in craving, as naltrexone extinguished conditioned responses to alcohol (Leavitt 2002). Coping-skills therapy in conjunction with naltrexone might be similarly beneficial for opioid-dependent persons.

Church and colleagues (2001) observed that 78% of patients used alcohol and other nonopioid drugs during naltrexone therapy. However, those with intermittent drug use actually fared better – in terms of medication compliance, treatment retention, and opioid avoidance – than those who were either immediately abstinent or habitual heavy users.

Other substances might be used as a coping mechanism, or alternate form of self-medication, while the patient is blocked by naltrexone from opioid effects. Church et al. (2001) proposed that this recommends a pragmatic perspective recognizing that occasional drug use may be a normal component of the recovery process for some persons. Further research is needed to determine if naltrexone dose adjustments or specific psychotherapeutic interventions could be helpful in dealing with the overall drug problem.

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Practice Implications

Although certain patients appear to be optimal candidates for naltrexone therapy, as described above (Table 2), it has been difficult to predict which individuals will be most receptive to this approach and will do well on it (Judson and Goldstein 1984). To date, there are no definitive guidelines for patient selection; however, if multiple treatment options are made available, patients may well select the modality that is best for themselves (Volpicelli and Szalavitz 2000).

Just as with the medication management of other serious chronic illness, a pragmatic strategy using naltrexone seeks to achieve remissions when possible, limit relapses, slow physical deterioration, and support patients in improving their quality of life. Patients completing opioid rehabilitation treatment should be educated to return to naltrexone in the event of opioid relapse or if they feel vulnerable to opioid use (Rawson and Tennant 1984).

Clinical Action Steps

In sum, there are several requirements for successful naltrexone therapy:

- achieving sufficient motivation in patients to begin treatment;
- successfully withdrawing patients from illicit opioids or methadone, and keeping them opioid-free until it is safe to start naltrexone;
- maximizing retention in treatment and compliance with taking naltrexone;
- involving family and/or significant others in the therapeutic process.

Treatment plans using naltrexone ideally respond to individual patient needs and, in that regard, practitioners may want to consider the following evidence-based conclusions:

1. Naltrexone is effective in a variety of treatment settings where motivation to stay in treatment, avoid opioid use, and take medications is supported by appropriate psychosocial therapy.
2. Therapy providing coping skills to identify triggers and avoid relapse if opioid and/or other drug use occurs may be more beneficial than a strict abstinence orientation.
3. Patients and their support persons need education on how naltrexone works and how to use it.
4. Individualized dosing quantities and flexible dosing schedules are possible and may be helpful.
5. Extended time in treatment while on naltrexone is beneficial, followed by “targeted” use of naltrexone as necessary for an indefinite period.

Presently available evidence indicates that, although naltrexone is not a cure for opioid dependence, it can be an essential component of a multifaceted program of rehabilitation. Outcomes for naltrexone-assisted treatments have varied; however, as Resnick (1998) has asserted, “for each individual protected from relapse, it is a 100% effective treatment.”

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