Chapter 5 --Clinical Profile

This chapter provides a brief overview of naltrexone as a medication, including its development and clinical role, its mechanism of action, its pharmacokinetic properties, its safety and common adverse effects, and some clinical precautions to be used in prescribing.

Development of Naltrexone

Naltrexone was approved by the Food and Drug Administration (FDA) in December 1994 as a potentially important tool in the treatment of alcohol dependence. At that time, its trade name was changed from Trexan®, which was first marketed by DuPont Merck Pharmaceutical Company in 1984 for use in treating opiate addictions, to ReVia® (Research Institute of Addictions, 1995). It is not, however, a new medication. Its history extends back to 1915, when German scientist Uber J. Pohl documented antagonistic effects of N-allylnorcodeine on morphine-induced respiratory depression in laboratory animals. The clinical importance of Pohl's finding was not pursued until the 1940s with the synthesis of nalorphine, the first synthetic opioid antagonist. Nalorphine was approved in 1951 for reversing the adverse and life-threatening effects of opiate overdose as well as for preventing narcotic-induced respiratory depression in obstetric cases and for diagnosing narcotic addiction (Gamage and Zerkin, 1973).

The theoretical basis for using opioid antagonists in the treatment of opiate dependence originated with the operant-conditioning formulations and experiments of Wikler and colleagues, beginning in the 1940s and continuing through the 1960s (e.g., Wikler, 1948; Wikler and Pescor, 1967). These researchers postulated that the euphoria accompanying the use of heroin and other narcotics reinforces repeated drug-seeking behavior as physical dependence develops. Once tolerance develops, the opiate-dependent individual avoids painful withdrawal symptoms by continuously increasing the amounts of opiates consumed. Even after addiction is overcome (i.e., abstinence established), a conditioned abstinence syndrome can be precipitated by environmental stimuli associated with the pleasurable effects of drug-taking. Thus, previously addicted individuals may again experience withdrawal symptoms when, for example, they return to old neighborhoods where drugs are available, encounter former "running partners," or come in contact with needles used to shoot up. These dysphoric responses are translated into a return of cravings for opiates.

If, however, the researchers hypothesized, an antagonist were used to block euphoric responses and the development of dependence, the reinforcing aspects of drug-taking could be attenuated, and the behavior would abate. Furthermore, if the antagonist also blocks conditioned responses, the powerful urge to take drugs again could gradually be decreased. Hence, with the help of concomitant psychosocial therapy, short-term administration of an opioid antagonist would give the detoxified addict time to

- Test the blockading effects if opiate use is resumed
- Extinguish "cues" that precipitate uncomfortable symptoms and craving
- Resolve problems resulting from addiction
- Regain some internal controls and personal responsibility for his or her behavior (Julius and Renault, 1976; Ginsburg, 1984)

This enticing theoretical construction prompted a more intensive search for a clinically acceptable opioid antagonist. The dysphoric side effects of nalorphine discouraged its use for this purpose. Cyclazocine—a benzomorphan derivative—was found to be orally effective and to have relatively long-acting opioid antagonistic effects, but a number of clinical trials during the 1960s were only partially successful in retaining patients because the medication also produced dysphoria as well as some withdrawal symptoms upon termination (Jaffe, 1967). Naloxone—an allyl derivative of noroxymorphone—was synthesized in the 1960s and found to be a sufficiently potent opioid antagonist without the dysphoric side effects. But naloxone’s duration of action after oral administration was found to be too short for clinical utility—24-hour blockade against a 50-mg challenge dose of heroin could not be achieved with 1,500 mg naloxone (Julius and Renault, 1976; Ginsburg, 1984; Gonzalez and Brogden, 1988). By comparison, naltrexone, which was also synthesized in the 1960s, was found to have several...
properties necessary for clinical utility in the treatment of opioid dependence:

- Long action
- Oral effectiveness
- Sufficient potency
- Few, if any, agonist properties
- Minor and tolerable side effects (Julius and Renault, 1976; Ginsburg, 1984)

Naltrexone is at least 17 times more potent than nalorphine in morphine-dependent humans and twice as potent as naloxone in precipitating withdrawal symptoms. A 100-mg oral dose of naltrexone given to abstinent addicts yielded a 90-percent blockade of subjective euphoria and other objective responses to intravenous heroin challenge at 24 hours, with antagonism to subsequent heroin challenges decreasing over 72 hours (Gonzalez and Brogden, 1988).

After encouraging findings in preclinical studies, naltrexone was extensively tested in clinical trials supported and encouraged by the new Special Action Office for Drug Abuse Prevention (SAODAP), a part of the Executive Office of the President that was created by Congress in the midst of a "heroin epidemic" and intense public pressure to solve the social and criminal problems stemming from drug addiction. In fact, the legislation that established SAODAP—a precursor to the National Institute on Drug Abuse (NIDA)—contained a special section and appropriations specifically targeted at the development of opioid antagonists (Julius and Renault, 1976).

Unfortunately, the promising expectations for naltrexone's efficacy and clinical utility in treating opiate dependence have not yet been fulfilled. NIDA, however, is currently studying ways to improve the effectiveness of naltrexone for treating opiate dependence.

Both controlled and noncomparative studies confirmed that naltrexone reduces heroin and other opiate self-administration and craving in detoxified opiate addicts, but attrition rates in most of these trials were very high, with many of the medicated subjects discontinuing naltrexone and relapsing to illicit opiate abuse (see Ginsburg, 1984; Gonzalez and Brogden, 1988; Julius and Renault, 1976; Mello et al., 1981). Highly motivated patients (e.g., professionals who had "everything to lose") were found to benefit most from naltrexone treatment, especially if medication was combined with strong family support and intensive, supportive psychotherapy (Gonzalez and Brogden, 1988). Because few "street addicts" met the screening criteria recommended for naltrexone treatment (i.e., employed, married, highly motivated to use nonopioid chemotherapy, and able to remain opiate-free for 5 to 10 days following withdrawal) and most abused more than one class of drugs, naltrexone only proved to be attractive to or effective for a limited cohort of patients who could be treated by knowledgeable treatment professionals.

Many of the findings from these NIDA-supported studies of naltrexone for the treatment of opiate dependence informed the clinical trials of the same drug for treating alcohol-dependent subjects. Notably, naltrexone—even in combination with psychosocial treatment—does not cure dependency. Clients must learn to be abstinent, avoid relapse, and improve their quality of life. Naltrexone is but one tool in a larger therapeutic regimen that must include individually tailored psychosocial therapy and rehabilitation focused on addiction-associated problems (Ginsburg, 1984).

**Pharmacological Properties**

**Pharmacodynamics**

Naltrexone hydrochloride—a relatively pure and long-lasting opioid antagonist—is a synthetic congener of oxymorphone with negligible opioid agonist properties (i.e., some pupillary constriction has been reported in isolated cases) (Gonzalez and Brogden, 1988). Naltrexone's major effects are produced by the parent drug (17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one) and its primary metabolite (6-beta-naltrexol). By binding competitively at opioid receptor sites within the central nervous system (primarily the brain), naltrexone prevents the stimulation of opioid receptors and thereby attenuates or completely blocks the usual euphoria-causing and physical dependence-producing responses. If opiates are already present (i.e., bound at receptor sites), then naltrexone displaces them almost immediately and precipitates such well-known withdrawal symptoms as anxiety, irritability, yawning, runny eyes and nose, perspiration, vomiting, cramps, tremors, and insomnia. If opiates are administered after naltrexone consumption, then the antagonist blocks both the pleasurable feelings and, with regular administration at sufficient doses, the development of physical dependence.

**Pharmacokinetics**
Dosing, administration, and tolerance

Clinical studies have shown that a 50-mg oral dose of naltrexone will block the pharmacological effects of a 25-mg dose of intravenously administered heroin for up to 24 hours. The results of other studies show that doubling the dose of naltrexone to 100 mg will block effects for up to 48 hours, and tripling the dose will block effects for up to 72 hours (PDR, 1997).

Flexible dosing schedules used in the clinical trials of naltrexone with opiate addicts have been acceptable to most patients and have proven equally satisfactory in other treatment settings. Dosing schedules have included regimens of 50 mg naltrexone on weekdays, with 100 mg on Saturday; 100 mg on Monday and Wednesday, with 150 mg on Friday; 150 mg on Monday and 200 mg on Thursday; or 150 mg every third day (Ginsburg, 1984; Gonzalez and Brogden, 1988). These schedules are typically used to make it easier for programs to supervise (i.e., observe) naltrexone ingestion in order to enhance medication compliance.

Naltrexone administration is not associated with the development of tolerance or dependence, and there are no withdrawal effects upon termination of naltrexone treatment (Addiction Research Foundation [ARF], 1996). Although the long-term effects of naltrexone are, as yet, not well documented, some research has shown that tolerance to the antagonist properties of naltrexone does not develop when administered for up to 21 months (Gonzalez and Brogden, 1988; ARF, 1996).

A double-blind, placebo-controlled study of naltrexone for treatment of opiate addicts found that 20 to 40 mg intravenous challenge doses of morphine administered after subjects had been taking naltrexone for a mean of 9.4 months produced dysphoric, histamine-like responses (Gonzalez and Brogden, 1988).

Alcohol-dependent persons who consume small-to-moderate amounts of alcohol while taking naltrexone may experience less euphoria than usual, but they will not have adverse, dangerous physical reactions to alcohol as seen with disulfiram. Naltrexone, however, does not prevent the impairment-causing effects of alcohol (e.g., loss of coordination, inability to exercise good judgment) and does not decrease blood alcohol levels resulting from drinking (Swift et al., 1994).

Absorption and bioavailability

Orally administered naltrexone is rapidly and nearly completely absorbed in the gastrointestinal tract (96 percent). Peak plasma concentrations of naltrexone (19 to 44 mg/L) and its primary metabolite 6-beta-naltrexol occur within 1 hour of dosing (Gonzalez and Brogden, 1988; PDR, 1997). Oral bioavailability estimates range from 5 to 60 percent (Gonzalez and Brogden, 1988).

Distribution

The volume of distribution for naltrexone following intravenous administration is estimated to be 1,350 liters. In vitro tests with human plasma show naltrexone to be 20 percent bound to plasma protein over the therapeutic dose range (PDR, 1997). There is no evidence of naltrexone accumulation in healthy subjects after multiple 100-mg daily doses (Gonzalez and Brogden, 1988). Both naltrexone and 6-beta-naltrexol are dose proportional in terms of Cmax (maximum concentrations) for the AUC (area under the curve) over the range of 50 to 200 mg (PDR, 1997).

Metabolism

The major metabolic pathway entails reduction of naltrexone to its major metabolite 6-beta-naltrexol, minor metabolites (e.g., 2-hydroxy-3-methoxy-6-beta-naltrexol and 2-hydroxy-3-methyl-naltrexone), and other metabolic products (Gonzalez and Brogden, 1988; PDR, 1997). Naltrexone is subject to significant first-pass metabolism in the liver, resulting in only an estimated 5 percent of the unchanged drug reaching the systemic circulation (Ginsburg, 1984; Gonzalez and Brogden, 1988). The systemic clearance (after intravenous administration) of naltrexone is approximately 3.5 L/min, which exceeds liver blood flow of approximately 1.2 L/min. This suggests both that naltrexone is a highly extracted drug (>98 percent metabolized) and that extrahepatic sites of metabolism exist. The mean elimination half-life values for naltrexone and the 6-beta-naltrexol metabolite are, respectively, 4 hours and 13 hours.

Early research demonstrated considerable individual variability in the metabolism of naltrexone. For example, in one study of acute and chronic administration of naltrexone, there was a three- to fourfold difference across subjects in peak 6-$-naltrexol levels, ranging from 83 to 288 ng/mL (Verebey et al., 1976). Findings also showed that narcotic antagonism was highly correlated with naltrexone plasma levels ($r = .90$). These early studies concluded that different individual biotransformation rates would be expected to influence the time course and magnitude of naltrexone blockade effects (Verebey, 1980).
Excretion

Both the parent drug and its metabolites are primarily excreted by the kidney (53 to 79 percent of the dose). Urinary excretion of unchanged naltrexone accounts for less than 2 percent of an oral dose, and fecal excretion is a minor elimination pathway. Urinary excretion of unchanged and conjugated 6-beta-naltrexol accounts for 43 percent of an oral dose. The renal clearance for naltrexone ranges from 30 to 127 mL/min, suggesting that renal elimination is primarily by glomerular filtration; the renal clearance for 6-beta-naltrexol ranges from 230 to 369 mL/min, which suggests an additional renal tubular secretory mechanism (Ginsburg, 1984; PDR, 1997).

Safety and Common Adverse Effects

Naltrexone appears to be clinically safe, with a low incidence of common adverse effects and no clinically significant changes in laboratory values among subjects being treated for opiate or alcohol dependency. Many of the adverse reactions and abnormalities that have been reported are common among patients for whom the drug is prescribed and have not occurred significantly more frequently in medicated cohorts compared with those receiving placebo (Ginsburg, 1984; PDR, 1997).

Prior to the FDA's initial approval of naltrexone as a treatment for opiate addiction, several studies showed naltrexone to be a safe, nontoxic medication in the single dosage range of 20 to 160 mg (Gritz et al., 1976; Julius and Renault, 1976; Judson et al., 1981; Mello et al., 1981). These findings have been supported in the more recent clinical trials of naltrexone as an adjunct for the treatment of alcohol dependence (Volpicelli et al., 1992; O'Malley et al., 1992; Croop et al., 1997).

Toxicity

No toxicity was found following daily administration of doses of up to 800 mg of naltrexone for a week (PDR, 1997).

Carcinogenesis

Animal studies have not found any carcinogenic responses to 2-year administration of naltrexone to rats (Gonzalez and Brogden, 1988; PDR, 1997).

Liver Damage

One of the most serious potential adverse effects of naltrexone is liver toxicity. High doses of naltrexone administered to obese patients (up to 300 mg/day or five times more than an effective blockading dose of 50 mg/day) have been found to produce hepatocellular injury in a substantial portion of exposed subjects (Gonzalez and Brogden, 1988). Although some of the obese patients in this study had mild abnormalities of liver function at baseline, elevated levels of serum aminotransferases returned to baseline or normal within a short time after termination of naltrexone treatment. It is important to note, however, that liver abnormalities are common among obese patients and those who are opiate- or alcohol-dependent (Gonzalez and Brogden, 1988).

High doses of naltrexone administered for treatment of Huntington's disease (up to 300 mg/day for up to 36 months) produced transient increases in serum aminotransferases (serum glutamic-oxaloacetic transaminase [SGOT] and serum glutamic-pyruvic transaminase [SGPT]) in 2 of 10 patients, but these elevations returned to baseline with continued treatment (Sax et al., 1994). These investigators concluded that chronic administration of naltrexone in doses up to 300 mg/day for periods up to 36 months does not significantly change hepatic function as measured by SGOT and SGPT levels.

In a more recent safety study of 570 heterogeneous alcohol-dependent patients (Croop et al., 1997), LFT results were similar to a comparison group of 295 patients who did not receive naltrexone (see below for further details of this study).

In the first clinical trial of naltrexone for the treatment of alcohol dependence, the medication was actually associated with lower levels of liver enzymes in the normal range compared with those of placebo-treated participants (Volpicelli et al., 1992, 1995a). Similar results were found in the second trial: Endpoint levels of aspartate aminotransferase and alanine aminotransferase were lower for the naltrexone-medicated subjects than for placebo-treated participants (O'Malley et al., 1992). Another study of heavy drinkers treated with naltrexone reported improved hepatic enzyme levels that were consistent with these earlier findings (Bohn et al., 1994). Better hepatic function in naltrexone-treated patients compared with placebo-treated patients is probably a reflection of reduced drinking among those receiving naltrexone, because alcohol is a known hepatotoxin.

Weight Reduction
Studies with small samples of naltrexone-treated subjects have noted some significant weight loss (Atkinson, 1984). Self-reports of weight loss were more common among naltrexone-treated patients than among placebo-treated patients (O'Malley et al., 1992). However, a 10-week, placebo-controlled trial with obese patients, using 50 to 300 mg daily doses of naltrexone, did not find any reduction in caloric intake or weight loss (Gonzalez and Brogden, 1988). A clinical trial of naltrexone plasma levels, clinical response, and effect on weight in autistic children found that although children in the highest weight percentile had a tendency to lose weight while taking naltrexone, none of the other children in the study were affected (Gonzalez et al., 1994).

Other Common Adverse Physiological Effects

Initial trials of naltrexone for treatment of opiate dependence found the medication to be well tolerated by most subjects, with few common adverse effects. The specific symptoms occurring more frequently in medicated patients than in placebo-treated controls participating in the first five double-blind trials included loss of appetite, nausea, vomiting, abdominal cramps, and constipation (Julius and Renault, 1976). A double-blind study comparing the efficacy of thrice-weekly 60- and 120-mg doses of naltrexone for opiate-dependent subjects found that neither toxicity nor complaints about side effects were significantly different from those in earlier studies using smaller (e.g., 50 mg) daily doses of naltrexone. Virtually all of the reported side effects seemed to mimic those of opiate withdrawal (e.g., gastrointestinal complaints) and decreased over the first 3 weeks of treatment (Judson et al., 1981).

Similar results have been found in the initial trials of naltrexone for treatment of alcohol dependence. The few reported physiological side effects, which are usually short-lived, primarily pertain to nausea, vomiting, headache, increased sexual desire, and increased anxiety and agitation (Volpicelli et al., 1992, 1995b). O'Malley and colleagues (O'Malley et al., 1992) found that naltrexone-treated patients experienced more nausea and reported more weight loss and dizziness than did subjects receiving placebo. The complaints usually followed the initial medication dose. A recent study of naltrexone as an adjunct to standard alcoholism treatment in a community clinic setting found that increased sexual desire was the only medication effect reported more frequently by the medicated patients compared with those taking placebo (Volpicelli et al., 1997). Overall, the common adverse effects of naltrexone have been severe enough to discontinue medication for 5 to 10 percent of alcohol-dependent patients who began taking the medication (Volpicelli et al., 1992; O'Malley et al., 1992; Croop et al., 1997).

A 3-month, open-label study sponsored by the DuPont Merck Pharmaceutical Company examined a heterogeneous sample of 570 naltrexone-treated alcohol-dependent men and women and 295 nonmedicated and nonrandomized controls to determine the safety and common adverse effects of this medication when taken for 3 to 6 months (Croop et al., 1997). The most common new-onset adverse events in the naltrexone group included nausea (9.8 percent) and headaches (6.6 percent). Other reported adverse effects included dizziness (4 percent), fatigue (4 percent), insomnia (3 percent), anxiety and nervousness (2 percent), and sleepiness (2 percent). In addition, a few patients reported abdominal pain and cramps, vomiting, low energy, and joint and muscle pain. Liver function test results were similar to those seen in the nonmedicated group. No unexpected adverse events were seen in this heterogeneous sample of individuals with alcohol dependence. This study is the largest to date describing the safety of naltrexone in a heterogeneous population of individuals with alcoholism. The investigators concluded that no new safety concerns were identified.

Common Adverse Psychological Effects

Naltrexone usually has no adverse psychological effects, and patients who take the drug do not report being either "high" or "down" while they are on this medication. Although it does seem to reduce alcohol craving, naltrexone is thought not to interfere with the experience of other types of pleasure (Dillon and Homer, 1995). Although two studies have assessed the psychological side effects of naltrexone (Gritz et al., 1976; Volpicelli et al., 1992), only the Gritz et al. study reported significant medication effects compared with placebo: (1) facilitation of attention and perception, as measured on the Cross-Out Test; and (2) mild euphoria, as measured on the Addiction Research Center Inventory.

Although further research is needed on many aspects of naltrexone's use, the evidence thus far is encouraging. Naltrexone appears to target the parts of the brain involved in alcohol abuse accurately and cleanly. The information in this TIP will help providers use this medication to better treat their patients who have alcohol use disorders.

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