TIP 28: Naltrexone And Alcoholism Treatment

Chapter 1 -- The Current Situation

Some 9.6 percent of men and 3.2 percent of women in the United States will become alcohol dependent at some time in their lives (Grant, 1992). The most recent National Household Survey on Drug Abuse estimates that about 32 million Americans had engaged in binge or heavy drinking (five or more drinks on the same occasion at least once in the previous month) and that about 11 million Americans were heavy drinkers (five or more drinks on the same occasion on at least five different days in the past month) (Substance Abuse and Mental Health Services Administration [SAMHSA], Office of Applied Studies, 1996). Alcohol-related disorders occur in up to 26 percent of general medical clinic patients, a prevalence rate similar to those for other chronic diseases such as hypertension and diabetes (Fleming and Barry, 1992). Alcoholics consume more than 15 percent of the national health care budget (Rice et al., 1990), seeking attention in medical settings for various secondary health problems (Schurman et al., 1985).

Researchers calculate that about 18 million Americans with alcohol abuse problems need treatment, but only one-fourth of them receive it (<u>Institute for Health Policy, 1993;</u><u>Institute of Medicine, 1996</u>). People suffering from alcohol disorders include teenagers, women, men, the employed or the unemployed, alone and isolated or part of a family, homeless or financially secure, and people of every race, creed, and level of education. People who have mental illness have a higher rate of substance abuse and alcoholism than everyone else; they also have a harder time getting help and staying in treatment. Recent tests on the medication naltrexone indicate that this drug can help many of those people. Naltrexone has been proven to decrease problem drinking--in some cases by almost half--when used with existing treatments, compared with other treatments used alone (O'Malley et al., 1992; Volpicelli et al., 1992, 1997).

The Evolution of Treatment

Today, alcoholism treatment generally consists of medical, psychological, and social interventions to reduce or eliminate the harmful effects of alcohol dependence and abuse on the individual, his or her family and associates, and others in society. Treatment approaches range from lower cost, less intensive methods (e.g., brief interventions/advice to stop or reduce drinking, referral to self-help programs) to higher cost, more intensive methods (e.g., inpatient detoxification and rehabilitation programs, residential treatment).

Many different orientations toward treatment, such as 12-Step, behavioral, motivational, medical, and spiritual, are used to various extents by treatment programs. A patient may need a different type of treatment at different stages in his or her life and in different phases of his or her addiction. There is no perfect way to treat every person, but research is under way to determine how to choose and apply the most appropriate treatment specifically to the particular needs of each patient.

Although the stigma attached to alcohol problems has abated, many still believe that alcohol problems represent a moral failing and that an alcoholic should be able to "white-knuckle" his or her way to sobriety. Such biases can be held by the patients themselves, by treatment providers with different backgrounds, by insurers, by communities, and by the legal establishment regionally. Those biases about the best way to treat substance abuse and dependence sometimes prevent patients from receiving adequate and appropriate care.

Understanding that the abuse of alcohol and other substances causes profound changes in brain chemistry and function may help to reduce the stigma and shame surrounding repeated relapse to alcohol abuse. Continued education and understanding should reduce the bias against the use of medications to treat the illness of substance abuse and dependence. As scientists continue mapping the brain, particularly those areas that govern pleasure and addiction, pharmacotherapies such as naltrexone will likely be used more often.

Development and Current Use of Naltrexone

Naltrexone was initially developed for the treatment of narcotic or opioid addiction, including heroin, morphine, and oxycodone (e.g., Percocet). Naltrexone is an opioid antagonist, which means that it blocks the effects of opioids. During the 1980s, animal studies revealed that opioid antagonists, including naltrexone, which the FDA approved in 1984 for treating opiate addiction, also decreased alcohol consumption by blocking certain opioid receptors (i.e., action sites) in the brain that help to maintain drinking behavior. Building on those laboratory findings, researchers conducted human clinical trials to determine whether naltrexone could play a role in the treatment of alcoholism (O'Malley et al., 1992; Volpicelli et al., 1992). The results of these studies suggest that naltrexone, when combined with appropriate psychosocial therapy, can effectively reduce craving and relapse rates in general populations of alcohol-dependent patients (Volpicelli, 1995). Based on such findings, the FDA approved naltrexone for use in the treatment of alcoholism.

Psychosocial treatments for alcoholism have been shown to increase abstinence rates and improve the quality of life for many alcoholics (<u>Miller and Hester, 1986</u>). Nonetheless, a significant proportion of alcoholics find it difficult to maintain initial treatment gains and eventually relapse to problematic drinking. When used as an adjunct to psychosocial therapies for alcohol-dependent or alcohol-abusing patients, naltrexone can reduce

- The percentage of days spent drinking
- The amount of alcohol consumed on a drinking occasion
- Relapse to excessive and destructive drinking

The National Institute on Alcohol Abuse and Alcoholism is currently funding over a dozen clinical trials with naltrexone, and a large-scale multisite study of naltrexone in combination with 12-Step facilitation therapy is being funded through the Department of Veterans Affairs.

Overview

The Consensus Panel that developed this TIP includes the country's leading experts on naltrexone. The Panel's aim is to provide counselors, treatment providers, clinicians, and the general public with a responsible, understandable assessment of the current data on the effectiveness and use of naltrexone for the treatment of alcoholism and alcohol abuse. Members of the Panel have drawn on the published literature, study findings that have been presented at conferences, and on their considerable clinical experience.

Chapter 2 is a "how to" chapter that covers the important clinical issues in using naltrexone as an adjunct to treatment. These issues include a review of eligibility considerations for naltrexone treatment, the initiation of treatment, ongoing treatment, and treatment termination issues. Chapter 3 details the basic neurobiological and preclinical research supporting clinical investigations of naltrexone for treatment of alcohol dependence. An overview of neurological reinforcement systems and drug dependence explains how naltrexone works. Chapter 4 describes the specific findings of the initial two clinical trials (O'Malley et al., 1992; Volpicelli et al., 1992) that established the efficacy of naltrexone in the treatment of alcohol dependence. It also describes subsequent research to identify the patients most likely to benefit from naltrexone treatment, the differential subjective effects of naltrexone, the use of naltrexone for other patient populations, naltrexone in the context of other pharmacotherapies, and directions for future research. Chapter 5 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 considerations when prescribing this medication.

The bibliography for this TIP appears in Appendix A. <u>Appendix B</u> guides clinicians or administrators who are interested in adding naltrexone to the formulary of their health care organization. Included in this appendix is an extensive list of Federal and private World Wide Web sites for readers who may want to access additional information about substance abuse treatment through the Internet. <u>Appendix C</u> details the process by which innovations are adopted over time and outlines strategies that encourage technology transfer and research utilization. For the organization that would like to incorporate naltrexone as a potential treatment adjunct, this appendix offers suggestions on how to prepare the system for this change. <u>Appendix D</u> provides two instruments to help treatment providers: The Obsessive Compulsive Drinking Scale and the Alcohol Urge Questionnaire.

It is important to remember that naltrexone may not be effective for every person with alcohol abuse disorder. In combination with other therapies, however, it can greatly improve outcomes for certain individuals. This TIP will help providers use naltrexone safely and effectively to enhance patient care and improve treatment outcomes.

Chapter2–Pharmacological Management With Naltrexone

Naltrexone therapy improves treatment outcomes when added to other components of alcoholism treatment. Treatment providers should tell patients that the medication is not a "magic bullet"; instead, naltrexone is likely to reduce the urge to drink and the risk of a return to heavy drinking. For patients who are motivated to take the medication, naltrexone is an important and valuable tool. In many patients, a limited period of naltrexone will assist in providing a critical period of sobriety, while the patient learns to stay sober without it. When starting naltrexone therapy, the treatment provider should consider eligibility, dosing strategies, medical considerations, ongoing monitoring, concurrent psychosocial intervention, and needs of special populations.

Naltrexone has few, if any, intrinsic actions besides its opioid-blocking properties: It does not block the physiological or psychological effects of any other class of drug. Because alcohol, like opiates, stimulates opioid receptor activity, naltrexone also appears to reduce the reinforcing/rewarding "high" that usually accompanies drinking. With the reduction in euphoria, alcohol consumption seems to be less rewarding. This may be one reason naltrexone works.

Eligibility for Treatment

Suitable Candidates

Naltrexone therapy is approved by the Food and Drug Administration (FDA) for use in individuals who have been diagnosed as alcohol dependent, are medically stable, and are not currently (or recently) using opioids (e.g., heroin, controlled pain medication). Because naltrexone is an addition to psychosocial support, appropriate candidates should also be willing to be in a supportive relationship with a health care provider or support group to enhance treatment compliance and work toward a common goal of sobriety.

Although it is not yet known who will succeed or who will fail when treated in this way, some studies suggest that those patients with high levels of craving, poor cognitive abilities, little education, or high levels of physical and emotional distress may derive particular benefit from the addition of naltrexone therapy to their psychosocial treatment (Jaffe et al., 1996; Volpicelli et al., 1995a). These are patients who often fail psychosocial treatments. Other factors such as family history of alcoholism and motivational status are unproven predictors of outcome but are currently being studied. Clearly, patient interest and willingness to take naltrexone are likely to be important considerations. Patients who have taken naltrexone before and quit because of nausea or headaches may be afraid to try it again. This is an opportunity for the treatment team to support and encourage the patient and to try a reduced-dose taper onto the drug.

Concurrent Psychosocial Interventions Are Necessary

Naltrexone has been approved as an adjunct to psychosocial treatment and should not be seen as a replacement of psychosocial interventions. Treatment is significantly more successful when the patient is compliant with both the medication and psychosocial programs (Volpicelli et al., 1997). Indeed, the efficacy of naltrexone in the absence of

therapy has not been studied. The use of therapy and naltrexone treatment in the same patient is not contradictory, and in fact, there is a potential for synergy. Psychosocial treatments are likely to enhance compliance with pharmacotherapy; likewise, pharmacotherapies, to the extent to which they reduce craving and help maintain abstinence, may make the patient more available for psychosocial interventions.

Barriers to Treatment and to Combination Treatment

The Consensus Panel acknowledges that there is much resistance to pharmacotherapy-from third-party payers, some addiction clinicians, and some self-help-oriented individuals who view medications as substituting a pill for self-empowerment and taking responsibility for the disease.

There are many reasons to believe that naltrexone is compatible with a range of psychosocial treatments for alcohol dependence, including 12-Step programs. Self-help groups support the use of nonaddicting medications in certain situations--it is important to emphasize that naltrexone is not addicting. In a multisite naltrexone safety study (DuPont Pharma, 1995), participation in community support groups was linked to good outcomes among patients receiving naltrexone. In completed or ongoing research, naltrexone has been used successfully as an adjunct to day hospital treatment, supportive psychotherapy, cognitive behavioral relapse prevention therapy, primary care counseling, and 12-Step facilitation therapy.

Some consider the cost of naltrexone a barrier. Naltrexone costs approximately \$4.50 per day or \$400 for a 3-month period. Additional costs include followup liver function tests (LFTs). In settings where patients do not routinely get physical examinations, the costs of these examinations will be added to the treatment costs. The daily cost of naltrexone, however, may be less than the cost of alcohol used by most patients, depending on which of the above costs are incurred by the patient.

However, for some alcoholism treatment programs that cover the costs of care for patients, these new costs may be difficult to absorb. On the other hand, there may be cost offsets in integrated systems, such as managed care systems or some hospitals. For example, if naltrexone reduces the risk of alcohol relapse, savings may occur in other medical costs associated with continued alcohol use such as detoxification services, poorly controlled hypertension due to medication noncompliance, and emergency room visits for alcohol-related injuries. For the individual, reduced alcohol consumption may result in an improved quality of life, as well as improvements in other areas including physical health, mental health, family and social relationships, and job performance. For the employer, cost offsets may result in fewer on-the-job problems and less absenteeism by employees who benefit from treatment. At this time, however, these potential cost offsets can only be proposed because formal cost-effectiveness studies have not yet been completed.

Importance of the Primary Care Physician

In primary care settings, large numbers of untreated individuals with the diagnosis of alcohol dependence may benefit from naltrexone therapy. Sixty percent of patients who are alcohol dependent will come to a primary care provider's office in a 6-month period for other reasons (Shapiro et al., 1984).

These patients represent an untapped reservoir of individuals who are not receiving needed treatment and who may be more readily treated in the primary care setting. Brief advice and monitoring by primary care providers can be effective in motivating problematic drinkers to reduce excessive drinking (for a review, see Bien et al., 1993). In compliant patients, the use of naltrexone is likely to enhance treatment outcome. The primary care provider may partner with other caregivers such as psychologists (Bray and Rogers, 1995).Figure 2-1 provides specific information on naltrexone for the primary health care provider.

Contraindications: Relative And Absolute

A contraindication for taking a prescribed medication is any symptom, circumstance, or condition that renders the medication undesirable or improper, usually because of risk.

There are two types of contraindications for naltrexone: *Absolute contraindications*, which refer to symptoms, circumstances, or conditions for which naltrexone unconditionally *must not* be prescribed, and *relative contraindications*, which refer to symptoms, circumstances, or conditions with varying degrees of risk that may preclude the administration of naltrexone.

Here is a common question: Significant liver disease is a relative contraindication to the use of other medications that may cause liver damage; but many alcoholics already have liver disease--can naltrexone still be used?

The answer is this: Because of the toxicity associated with alcohol, liver abnormalities are common among alcohol-dependent patients (Gonzalez and Brogden, 1988). Although initial blood tests may indicate some hepatic (i.e., liver) dysfunction and therefore potential risk, reductions in drinking resulting from treatment combining naltrexone therapy may lead to improved liver function. Even so, LFTs should be performed regularly to ensure that no damage is being done and to guide clinical care. Similarly, many patients who will benefit from naltrexone treatment have chronic hepatitis B and/or hepatitis C; a controlled, randomized, prospective study of such hepatitis patients showed no significant difference in LFT results with naltrexone at the recommended doses (Lozano Polo et al., 1997).

Another question is what to do when circumstances arise in patients already taking naltrexone that would put the patient at risk for harm if naltrexone treatment is continued. These circumstances might include, for example, pregnancy or new infection with viral hepatitis. Individuals who acquire new relative or absolute contraindications should stop taking naltrexone and be reevaluated. Figure 2-2 provides a list of absolute and relative contraindications for naltrexone.

Naltrexone and the liver

Although naltrexone has few absolute contraindications, high doses of naltrexone (300 mg/day) may lead to elevations in serum bilirubin and liver enzymes (e.g., <u>Gonzalez and Brogden, 1988; Sax et al., 1994</u>). For this reason, the medication is contraindicated for patients with acute infectious hepatitis or patients with liver failure. (For a review of clinical studies on naltrexone and liver damage, see <u>Chapter 5.</u>)

The Consensus Panel recommends caution in using naltrexone in patients whose serum aminotransferases results are over three times normal. In these patients, more frequent monitoring of LFTs should be considered. In general, improvements in liver function are expected if the patient responds to therapy and maintains abstinence. Physicians experienced in the use of naltrexone have given it safely to patients with significantly elevated serum aminotransferases. Because total bilirubin reflects more severe and potentially chronic liver dysfunction, the Consensus Panel recommends using total bilirubin to both evaluate and monitor the development of liver problems. A hepatologist may be consulted prior to beginning naltrexone therapy in patients with elevated total bilirubin.

Another issue clinicians should consider before determining a patient's eligibility for naltrexone therapy is that alcohol alone may be responsible for pretreatment elevated LFT results. In some cases, simply stopping the consumption of alcohol will immediately lower LFT values appreciably. When there is a question, the Consensus Panel recommends repeating LFTs after 5 to 7 days of abstinence. If the levels dramatically improve, then the patient may prove to be a suitable candidate for naltrexone. Research supports this observation: In a number of the treatment studies, LFTs in the group receiving naltrexone improved over those not receiving naltrexone, presumably because of the reduction in their drinking (O'Malley et al., 1992; Volpicelli et al., 1992, 1995a, 1997).

As with many disorders, the final decision to use naltrexone should be based on a riskbenefit analysis. Clinician and patient may choose to start naltrexone treatment in spite of the presence of medical problems because the potential benefits of reducing or eliminating alcohol consumption may outweigh the potential risk of naltrexone.

When the patient uses pain medication or heroin

It is important to focus not just on alcohol use but also to address the use of other substances--particularly illegal opiates and opioid-containing medications--that may pose the same level of concern and possible adverse consequences. The use of other substances can be evaluated by random urinalysis, collateral reports from family members or employer (with the patient's written consent), and self-reports from the patient. In addition to illegal substances, the use of both prescription and nonprescription medications is an important issue and should also be addressed. In this regard, the patient's agreement or resistance to continuing treatment may indicate his or her level of willingness to consider other substance use as a problem.

Because of its opiate antagonist properties, naltrexone may cause or worsen opiate withdrawal in subjects who are physiologically dependent on opiates or who are in active opiate withdrawal. Thus, naltrexone is contraindicated in these patients until after they have been withdrawn from opiates for at least 5 to 10 days, or longer if they are withdrawing from methadone without benefit of buprenorphine (Buprenex) (once approved). (Naltrexone is sometimes used with clonidine and close medical monitoring as an opiate withdrawal method; see O'Connor and Kosten, 1998, for a review). Similarly, naltrexone is absolutely contraindicated in patients currently maintained on methadone or LAAM for the treatment of opiate dependence.

Although the anticipated need for opioid medications on the basis of an identified medical problem is a relative contraindication for the use of naltrexone, it will not always preclude the use of naltrexone by someone struggling to stop drinking. Rather, particularly for chronic pain disorders, a reduction in abusive drinking may help reduce pain and disability and obviate the need for opioid analgesics.

If at any time the need for opioid treatment becomes necessary, naltrexone therapy can be discontinued for 2 or 3 days, and the opioid can then be given in conventional doses. If opioids are needed to reduce pain in someone with recent naltrexone ingestion, pain relief can still be obtained but at higher than usual doses. These doses require close medical monitoring (see the section on pain management later in this chapter).

The opioid blockade produced by naltrexone is not immediately reversible but is potentially surmountable by very high doses of opiates. Patients should be warned that self-administration of high doses of opiates while on naltrexone is extremely dangerous and can lead to death from opioid intoxication by causing respiratory arrest, coma, or circulatory collapse. In emergency situations requiring opiate analgesia, a rapidly acting analgesic with minimal respiratory depression should be used and carefully titrated to the patient's responses.

Pregnancy

Women should be tested for pregnancy before initiating naltrexone and advised to use a reliable form of birth control. Data on the use of naltrexone during pregnancy are so scant that the risks are basically unknown. In laboratory animals, naltrexone has been shown to have an embryocidal effect when given in extremely high doses (approximately 140 times the human therapeutic dose). Consequently, naltrexone is classified by the FDA as a Category C drug, which denotes

There are no adequate and well-controlled studies in pregnant women. reVia [naltrexone] should be used in pregnancy only when the potential benefit justifies the potential risk to the fetus (Physicians' Desk Reference [PDR], 1997, p. 958).

Naltrexone has been shown to have effects on a number of hormones, including growth hormone, luteinizing hormone, and prolactin. In light of these effects, the Consensus Panel generally recommends against the use of naltrexone during pregnancy or while mothers are nursing their babies. The risks of fetal alcohol syndrome (FAS) and other

alcohol-related birth defects are high for the offspring of women who continue to abuse alcohol. Therefore, it is essential that the pregnant patient receive treatment in one of the many excellent programs available and maintain his or her sobriety to protect the health and future well-being of her fetus. (More information is available from the Centers for Disease Control and Prevention, FAS Prevention Section, 770-488-7370, or e-mail at *ncehinfo@cdc.gov.*) \uparrow TOP

Adolescents

The use of naltrexone in adolescents is considered a relative contraindication because there are no data available about the safety and efficacy of naltrexone in this population: Naltrexone has been mostly studied in individuals 18 years of age and older. The known effects of naltrexone on the human hormonal system--including growth hormone, luteinizing hormone, and prolactin-- are particularly important considerations in adolescents because they have not reached full maturity. As a result, naltrexone is not recommended for children who have not reached puberty, and careful consideration of the potential benefits and risks should be given prior to using naltrexone in postpubescent individuals.

Naltrexone and Other Substances

Drug-drug interactions

With the exception of opiate-containing medications, formal drug interaction studies have not been done. However, caution should be used when combining naltrexone with other drugs associated with potential liver toxicity, such as acetaminophen and disulfiram (Antabuse). Other interactions of which Consensus Panel members are aware include thioridazine (Mellaril; based on case reports of oversedation) and oral hypoglycemics (based on case report data). The Consensus Panel suggests that clinicians be watchful of drug-drug interactions and report them to the manufacturer(s) if they do occur. Based on the results of a large multisite safety study recently conducted by the manufacturer (Croop et al., 1997), concurrent use of antidepressants and naltrexone appears to be safe. *** TOP**

Interaction with alcohol

Unlike disulfiram, naltrexone does not appear to alter the absorption or metabolism of alcohol and does not have major adverse effects when combined with alcohol. Some patients, however, have noted increased nausea caused by drinking alcohol while taking naltrexone. There is good evidence that naltrexone reduces the likelihood of continued drinking following a lapse and decreases the amount of alcohol consumed if there is a "slip" during treatment. However, naltrexone does not make people "sober up" and does not alter the acute effects of alcohol on cognitive functioning (Swift et al., 1994).

Starting Treatment

Patient Education Comes First

When starting a new medication, the patient needs to understand how it works and what to expect while taking it. Particularly with naltrexone, treatment providers need to offer that information and guidance to patients. Pamphlets for patients and providers as well as copies of research reports on naltrexone can be requested free of charge from DuPont Merck (1-800-4PHARMA), the company that currently markets naltrexone (under the trade name ReVia).

The provider should negotiate a treatment plan with the patient at each stage of therapy. Patients need to know that they may experience protracted effects from their alcohol use and from alcohol withdrawal, and that they may not feel well for some period of time. They should understand that symptoms from alcohol withdrawal are similar to common adverse effects from naltrexone administration, and thus it is often difficult to determine which symptoms are caused by naltrexone. When patients do not feel well, it is a challenge to keep them in treatment. Providers should educate patients so they can better manage their own concerns and anxieties.

Most patients are willing to take naltrexone if they believe it works. This has implications for provider education as well: If alcoholism treatment clinicians and counselors do not believe the medication is effective, then they can hardly be expected to provide a convincing education for the patient. All clinicians should have access to accurate information concerning naltrexone treatment. This TIP provides such information and is free to anyone who requests it. **^ TOP**

Initial Medical Workup

An initial medical workup must be completed before naltrexone treatment can begin. The pretreatment workup should include a physical examination, laboratory tests, medical and substance use/abuse histories, and a mental health/psychiatric status screen. A physical examination of the liver and various laboratory tests, including LFTs, pregnancy test, and urine toxicology screen, are also part of the medical workup. A complete/updated medical history helps to rule out possible contraindications. A substance abuse history should focus on the use of other substances, especially opiates, as well as the patient's history of use, misuse, or abuse of prescribed medications. Screening for signs and symptoms of substance use provides an added check to the substance abuse history and results of the urine toxicology screen. For example, intravenous use is associated with needle marks; hard blackened veins; and abscesses in the arms, hips, buttocks, thighs, or calves. Inhaled drugs often cause a brown tongue, nasal septum abnormalities, or unexplained diffuse wheezes. Illicit drug use can lead to unexplained severe constipation, agitation, repeated requests for prescriptions for controlled substances, and a desperate need to leave the office after several hours.

The presence of co-occurring mental disorders with alcohol dependence may negatively influence the outcome of alcoholism treatment if the coexisting mental disorders are not adequately treated. Therefore, a mental health/psychiatric status screening should also be part of the pretreatment workup. Positive screens may necessitate more formal mental status examinations to determine the severity of the illness and the appropriate course of

treatment. The Consensus Panel recommends focusing the psychiatric interview on anxiety symptoms, depression, psychosis, and cognitive functioning because these elements may complicate therapy. <u>Figure 2-3</u> summarizes the elements of a pretreatment workup.

The literature accompanying naltrexone suggests the use of a naloxone (Narcan) injection challenge test in patients for whom continued opioid use is suspected but not proven. This challenge test is easily performed in the office by administering subcutaneously 0.1 mg of naloxone and monitoring the patient for withdrawal symptoms, including sweating, nausea, cramps, vomiting, extreme discomfort, runny eyes and nose, and so on. If no symptoms are seen within 5 minutes, then the test is negative and naltrexone may be given orally. The Consensus Panel, however, believes that the use of this test is usually not necessary for alcohol-dependent patients--in most cases, a careful patient history asking directly about opioid use (including pills, snorting, and smoking recreationally) and a urine toxicology screen for opioids is sufficient.

The Consensus Panel suggests that while gathering patient history, providers and counselors should evaluate potential constraints to honesty: A patient may not tell the truth if a parent, spouse, or probation officer is present. On the other hand, a family member may be able and willing to provide more accurate and honest information about a patient's history.

Pretreatment Abstinence

Naltrexone should be initiated after signs and symptoms of acute alcohol withdrawal have subsided. However, no formal studies have examined the effect of giving naltrexone during acute alcohol withdrawal. Until more definitive information on this issue is available, the Consensus Panel recommends that patients be abstinent for 3 to 7 days before initiating naltrexone treatment. The shorter time frame is designed to accommodate standard 3-day detoxification programs. Studies to date have shown naltrexone's effectiveness only among patients with at least 5 days of abstinence, although naltrexone has been used in patients who are actively drinking.

Initiation of abstinence can be accomplished in a variety of settings. However, providers should follow standard protocols for alcohol detoxification, including the use of the usual medications as needed, vitamins, and monitoring for alcohol withdrawal to prevent delirium tremens, seizures, and Wernicke's encephalitis. The American Society of Addiction Medicine's *Patient Placement Criteria for the Treatment of Substance-Related Disorders*, Second Edition (American Society of Addiction Medicine, 1996), and TIP 19, *Detoxification from Alcohol and Other Drugs* (Center for Substance Abuse Treatment [CSAT], 1995), provide detailed information about matching patients to appropriate levels of care, as well as step-by-step clinical detoxification guidelines.

Starting Doses

The FDA has established guidelines for the dosage and administration of naltrexone. The use of naltrexone in actual clinical practice, however, is in an evolving state and continues to be tested and modified by treatment providers. Factors influencing how and when naltrexone is used include the patient population being treated, the severity of alcohol dependence, and the requirements of the institutional system in which treatment takes place. Within general parameters, treatment with naltrexone must be individualized according to these factors as well as to the particular needs of each patient.

The FDA guidelines recommend an initiation and maintenance dose of 50 mg/day of naltrexone for most patients, usually supplied in a single tablet <u>(see PDR, 1997)</u>. Although patients generally tolerate the drug well at this dose, approximately 1 in 10 patients will experience nausea or headache. Preliminary evidence indicates that certain patients--such as women, younger patients, and those who have had a short duration of abstinence before treatment initiation--may experience a somewhat higher rate of nausea with naltrexone treatment (O'Malley et al., 1996c). Adverse events may make the patient reluctant to continue the medication.

In practice, the starting dose is often reduced for several days or divided in two, to prevent initial nausea and other adverse events that sometimes occur. For example, treatment can begin with either one-quarter of a tablet (12.5 mg/day) or one-half of a tablet (25 mg/day) daily, with food, and eventually move to a full tablet daily (50 mg/day) within 1 to 2 weeks if tolerated. The brief period of abstinence prior to beginning naltrexone may also help reduce the risk of adverse effects. Of course, if significant adverse effects occur after an initial dose, lower doses should be tried after a rest period of a few days. These suggestions for dosing strategies are summarized in Figure 2-4.

Management of Common Adverse Effects

In a recent large multisite safety study <u>(Croop et al., 1997)</u>, the following individual adverse events were reported by 2 to 10 percent of the patients: nausea, headache, dizziness, fatigue, nervousness, insomnia, vomiting, and anxiety (see <u>Chapter 5</u> for more details of this study). Because these adverse effects are generally brief in duration and uncomfortable but not harmful, management always includes giving patients coping strategies and focusing on the positive aspects of naltrexone treatment. Education prior to starting naltrexone is helpful, with the caution that some patients are already afraid, anxious, and susceptible to suggestion. Many of the common adverse effects--notably headaches, nausea, and anxiety--may overlap with symptoms experienced during alcohol withdrawal, so that it is often difficult to assess whether the effects are due to the medication or to the underlying withdrawal.

The Consensus Panel recommends the following strategies that providers can implement to reduce common adverse effects:

• **Patient education**. If patients are going to experience common adverse effects, these tend to occur early in treatment, and the symptoms generally resolve within

1 to 2 weeks. Support and reassurance can help patients better tolerate these transient adverse effects.

- **Timing of doses**. Because common adverse effects may worsen during nicotine withdrawal, patients who smoke should not take naltrexone immediately after waking up. For all patients, naltrexone should ideally be taken after the "regular" morning routine, preferably around breakfast time with food. Individual patient needs can guide the timing of doses: Fatigue suggests an evening dose, whereas sleeplessness suggests a morning dose.
- **Split dosage**. The Consensus Panel recommends morning dosing for most patients in order to establish a routine and ensure better compliance. However, if there is a need to split the dose, then it will be important to help the patient establish a good routine for dosing later in the day, especially if the patient is not in stable housing. One simple way is to take half a pill with breakfast, and then take the second half with dinner.
- **Dose reduction**. Strategies for controlling persistent nausea or other adverse events include dose reduction, slow titration, and cessation of the medication for 3 or 4 days and then reinitiating it at a lower dose.
- Management of nausea. Nausea is a problem for approximately 10 percent of patients and may reduce compliance. To minimize nausea, patients should be advised to take naltrexone with complex carbohydrates such as bagels or toast and not to take the medication on an empty stomach. The use of a tablespoon of simethicone (e.g., Maalox) or bismuth subsalicylate (e.g., Pepto-Bismol) before taking naltrexone may help. Dose reductions as described above should also be considered.
- Withdrawal. Patients may not be able to discriminate between the common effects of withdrawal from alcohol and the common adverse effects caused by naltrexone. The key is to encourage patients and to reassure them that these symptoms should get better with time. Alcohol withdrawal can be managed with support or benzodiazepines if indicated (see TIP 19, *Detoxification from Alcohol and Other Drugs;* CSAT, 1995).

↑ TOP Ongoing Treatment With Naltrexone

Maintenance Doses

The currently recommended maintenance dose of naltrexone is 50 mg/day. However, maintenance doses of less than the standard 50 mg/day regimen may be considered in patients who do not tolerate the standard maintenance dose but who are otherwise good candidates for naltrexone. It is preferable to decrease the maintenance dose to 25 mg/day to avoid noncompliance and relapse due to common adverse effects rather than to rule out naltrexone as a treatment option for these patients. Some patients may ask to take naltrexone twice daily in order to experience subjective relief from craving. In these cases, the same daily dose may be divided in two and given at those times of the day when craving is strongest.

Under certain circumstances, providers may increase the daily naltrexone dose to greater than 50 mg. Patients who may be considered for an increase include those who report persistent feelings of craving, discomfort, and even brief relapses, despite compliance with their treatment plan. In such cases, dosages of 100 mg/day are sometimes used, with appropriate medical monitoring. There is evidence that naltrexone is well tolerated, safe, and effective at these higher doses (McCaul, 1996), except with some very obese patients (Gonzalez and Brogden, 1988). For patients who miss occasional doses, higher naltrexone doses may provide greater protection. Compliance enhancement techniques are currently being evaluated, which may eventually reduce the number of missed doses. As the number of missed doses decreases, the patient may be able to return to previous, lower dosages.

Before adjusting dosage, providers should first consider intensification of other treatment interventions, particularly psychosocial components. The reason that the medication is not working should be explored. For example, adverse effects may lead to skipped doses and would suggest the need for a lower rather than higher naltrexone dose. Conversely, a patient's request may sometimes be justification enough for a dose increase, especially in those who are at high risk for relapse. It is preferable to increase the dose in anticipation of, rather than in response to, relapse. Naltrexone is not a drug of abuse, and providers should view a patient's request for increased dose as a sign of engagement and motivation in treatment, not as drug-seeking behavior.

In some outpatient treatment settings (see Oslin et al., 1997, and studies of patients addicted to opiates), higher doses of naltrexone have been given under observation either 2 days a week or 3 days a week. If this is necessary and the patient tolerates a higher dose, then the protocol typically is Monday 100 mg, Wednesday 100 mg, and Friday 150 mg.

Duration of Treatment

The goal for the patient taking naltrexone is to eventually discontinue the medication without relapsing. It would be a mistake to assume--or to mislead patients--that somehow the medication, rather than the patient him- or herself, will do the work of achieving and maintaining the goals of treatment. It must be remembered that alcoholism is a chronic disease and, like most chronic diseases, is likely to require continued monitoring to maintain lifelong remission of the disease.

Although FDA guidelines indicate that naltrexone should be used for up to 3 months to treat alcoholism, the Consensus Panel recommends that treatment providers individualize the length of naltrexone treatment according to each patient's needs. Initially, the patient can be treated with naltrexone for 3 to 6 months, after which the patient and the therapist can reevaluate the patient's progress.

At this time, the decision to extend treatment must be based on clinical judgment. Although the results of studies on the efficacy of other durations of naltrexone treatment for alcohol dependence are forthcoming, naltrexone has been used for extended periods ranging from 6 months to several years in the treatment of opiate addiction, suggesting that longer term treatment is safe. Safety data have been presented on the use of naltrexone in alcohol-dependent patients up to 1 year with no new safety concerns noted (Croop and Chick, 1996).

Pending definitive research results, the Consensus Panel concurs that certain patients may be appropriate candidates for long-term (e.g., up to 1 year) naltrexone treatment if they demonstrate evidence of compliance with medication and psychosocial treatment regimens. Factors to be weighed in the clinical decision to extend treatment beyond 3 to 6 months include the following:

- **Patient interest**. Continued patient interest in taking naltrexone is usually an indication that the patient is engaged in treatment and perceives the medication as helping maintain his or her sobriety. Patients who wish to continue naltrexone treatment after an initial period of sustained abstinence may be considered for long-term treatment.
- **Recent dose adjustments**. Although the duration of treatment should always be individualized, it is generally recommended that naltrexone treatment can be discontinued after 3 to 6 months of sustained abstinence. Thus, when a clinical response has been achieved only recently, naltrexone treatment can continue for at least another 3 months in order to provide optimal care.
- **Partial treatment response**. Some patients have a partial response to naltrexone treatment. Examples are a patient who achieves a reduction in drinking but continues to have episodes of clinically significant drinking, or one who progresses toward treatment goals without achieving sufficient stabilization. These patients may be appropriate candidates for additional naltrexone treatment and dose adjustments. In general, the success of treatment must be measured across a spectrum of outcomes; failure to achieve total abstinence should not be considered synonymous with failure of treatment.
- **Prophylaxis in high-risk situations**. Although established data are currently lacking, some animal studies (e.g., Reid et al., 1996) and a recent open-label clinical study (Kranzler et al., 1997) suggest that after an established course of daily treatment, naltrexone may be effective on an intermittent or as-needed basis. In certain circumstances, continued naltrexone treatment may be considered as prophylaxis for patients who anticipate a high-risk situation or who undergo major stressors or lifestyle changes that increase the risk of relapse.

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Other Clinical Considerations During Treatment

Followup liver function tests

After the initial screening, followup LFTs should be completed after 1 month of naltrexone treatment. If the results are acceptable, followup LFTs may then be conducted at 3 and 6 months after the initiation of treatment, depending on the severity of liver dysfunction at the start of treatment.

More frequent monitoring is indicated for cases in which dose adjustments are being made, baseline LFTs are high, there is a history of hepatic disease, disulfiram or other potential hepatic-toxic medications are added to the treatment, or symptomatology indicates the need for monitoring. Prescribing physicians should also educate the patient regarding the signs and symptoms of hepatic toxicity (white stools, dark urine, yellowing of eyes). A clinically significant increase (three to five times or more) over recent LFT results or an elevation in bilirubin signals a need for discontinuation, as do other clinical signs of hepatic toxicity. In such cases, the treatment provider should discontinue naltrexone treatment, sort out the causes for the increased LFT results, and retest the patient before reinstating the medication.

The Consensus Panel suggests that some clinicians may want to monitor LFTs as a clinical indicator of treatment response and also as a form of encouragement for patients. LFTs can be used to verify self-reports of drinking and to encourage patients whose enzyme levels show improvement.

Pregnancy

During treatment, female patients should be instructed to inform their caregivers if they suspect that they may be pregnant or experience a delay or change in their menstrual cycles. If a patient becomes pregnant, naltrexone should generally be discontinued.

Pain management

Naltrexone is an opioid antagonist and will, therefore, block the effects of usual doses of therapeutic opioids, including codeine, hydrocodone bitartrate, oxycodone hydrochloride, morphine, and meperidine hydrochloride (Demerol), among others. If the patient has a pain condition that requires treatment, providers should use nonnarcotic methods of analgesia as first line of treatment if possible. Naltrexone will not reduce the effectiveness of nonnarcotic analgesics (i.e., nonsteroidal anti-inflammatory medicines, spinal blocks, general and local anesthesia). If narcotic pain relief is indicated, patients must discontinue naltrexone use for the period during which analgesics are required. If a painful event is anticipated, such as scheduled surgery or dental work, naltrexone should be discontinued 72 hours prior to the procedure. If a patient is taken off naltrexone and put on an opioid analgesic, he or she should be abstinent from the narcotic for 3 to 5 days before resuming naltrexone treatment, depending on the duration of opioid use and the half-life of the opioid. A more conservative approach is to wait 7 days. Alternate methods are to administer the naloxone challenge test or to titrate the naltrexone dose and observe patient reactions. Again, these decisions should involve a risk-benefit analysis and should incorporate the patient's need for addiction treatment.

In emergencies such as cases of acute severe pain, higher doses of opioid analgesics may be used with extreme caution to override the blockade produced by naltrexone. The narcotic dose needs to be carefully titrated to achieve adequate pain relief without oversedation or respiratory suppression. Both the dose and the patient's vital signs (including respiratory rate, level of awareness, and level of analgesia) must be closely monitored. The capability of respiratory assistance and support must be available, should this be necessary.

Patients with chronic pain that does not respond to nonnarcotics are not candidates for naltrexone treatment. Therefore, patients with sickle cell disease, hemophilia, recurrent kidney stones, or other high-risk conditions (e.g., advanced cancer or chronic pancreatitis from alcoholism) requiring narcotic analgesia also are not good candidates.

Finally, the Consensus Panel notes that issues of pain management and emergency treatment--for which a patient is likely to come under the care of someone other than the primary care provider--underscore the importance of issuing safety identification cards to patients on naltrexone (see Figure 2-5). These cards provide information that the patient is receiving naltrexone and instructions for treating patients in the event of an emergency. These cards are available for free to clinics from the manufacturer of naltrexone (1-800-4PHARMA), or they can be prescribed from the pharmacy with the first dose. If such a card is not on hand, provide the patient with the physician's card, including the patient's name, and state in large print that naltrexone is being taken; include a 24-hour telephone number for the prescribing physician's service.

Continued drinking

Although abstinence is the goal of naltrexone therapy, some patients who are compliant with treatment may continue to drink alcohol periodically. This is not a sufficient reason to discontinue naltrexone: Some patients respond to naltrexone treatment at first by reducing rather than stopping their drinking. Total abstinence should be a long-term goal, not a condition of initial treatment. Most treatment programs are generally tolerant of incremental steps toward that goal, while setting good boundaries for patients who are relearning how to live without alcohol.

When a patient drinks during treatment, the clinician should evaluate whether the patient is taking his or her medication regularly and participating in treatment actively, because these factors are related to treatment improvement (Volpicelli et al., 1997). Alcohol treatment programs have many skills and strategies for improving compliance, all of which should be explored with the patient. For example, the patient's routine for taking medication can be reviewed and modified. The intensity of care along with the expectations placed on the patient may also be stepped up. This may include stepping up the frequency of sessions or attendance at self-help groups or support group meetings. As discussed earlier, dose adjustments may also be indicated. Prescription refill frequency may be changed, and the medication may be dispensed in blister packs to improve compliance. Each physician working with a treatment program must participate in the reevaluation of the goals of treatment and those of the patient in order to decide how to proceed. Direct communication between the treatment team and the physician is another key to success.

The ways in which treatment programs use disulfiram with naltrexone vary according to treatment goals and institutional policies. Some examples of models of dual therapy are as follows:

- Primary use of disulfiram, with naltrexone introduced to abate persistent complaints of craving
- Initial use of disulfiram to establish a period of abstinence prior to initiating naltrexone therapy, then discontinuing disulfiram
- Use of disulfiram as prophylaxis in high-risk situations in patients taking naltrexone
- Short-term use of disulfiram in patients who have continued to drink periodically in order to help them break this cycle and achieve a sustained period of abstinence

The safety and efficacy of concomitant use of naltrexone and disulfiram are unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks. Patients should always check with the prescribing physician about any medications taken with naltrexone.

If naltrexone is used with disulfiram, then treatment providers should perform LFTs shortly after the initiation of combined use of disulfiram and naltrexone. Providers should retest patients every 2 weeks for 1 to 2 months and then at regular intervals, such as monthly, thereafter. Combination therapy with disulfiram and naltrexone is not used for very long periods, and generally the two drugs are not started simultaneously. **↑** TOP

Ending Naltrexone Therapy

Successful Termination Of Naltrexone

The usual naltrexone dose of 50 mg/day can be discontinued without tapering the dose because there is no withdrawal syndrome associated with naltrexone therapy. The same appears to be true for higher doses of naltrexone. Nonetheless, dose reductions may be useful psychologically for some patients. For example, patients might begin to take the medication every other day, and then at times of greatest risk for drinking (e.g., weekends, social gatherings), and then discontinue the medication altogether. A similar strategy has been used successfully with calcium carbimide(<u>Annis and Peachy Peachey, 1992</u>) and is currently being investigated for naltrexone(<u>Kranzler et al., 1997</u>). The treatment team should work with the patient in developing Whenever possible, treatment providers also help the patient's family prepare for treatment closure. It is important for both the patient and the family to recognize the components of treatment that have been successful in helping the patient to maintain sobriety, including the patient's own efforts, newly acquired skills, and the active support of his or her family.

Monitoring the Outcome Of Treatment

In evaluating the outcome of naltrexone therapy, providers should expect to see evidence of positive improvement over time as evaluated by the treatment program's indicators of progress. The following lists some of the possible criteria that can be used and selected to fit each program's needs and policies:

Compliance with treatment plan. Areas of patient compliance include keeping appointments for medication monitoring, prescription refills, counseling sessions, and group meetings, as well as keeping agreements about payment for treatment. Naltrexone is clinically effective compared with placebo when the patient is highly compliant, that is, taking the medication as prescribed, and completing psychosocial treatment as planned (Volpicelli et al., 1997).

Stable abstinence or significant reduction in the frequency and amount of drinking. Studies suggest that long-term outcomes are better for patients who maintain abstinence during treatment (O'Malley et al., 1996a). Alcoholics Anonymous (1976) or other self-help groups can help support this as an outcome. Improvements should be confirmed by the following:

- 1. *Patient self-reports*. The patient's own self-reports can be useful indicators of treatment success. The provider should initiate a discussion with the patient about the quantity and frequency of drinking, especially during stressful periods (e.g., holidays, major life changes).
- 2. *Collateral reports*. Those in regular contact with the patient, such as family members and employers, can provide confirmatory reports of the patient's sobriety. The treatment provider must obtain the patient's written consent before communication with these individuals takes place. Such collateral reports may be useful, but it is important to bear in mind that although they can tell the provider whether the patient has been drinking, they rarely provide insight into the quantity and frequency of drinking and thereby whether the patient has experienced an actual relapse.
- 3. *Biological markers*. Although a new marker of recent drinking--carbohydratedeficient transferrin--is on the horizon and may prove to be a more accurate marker than serum aminotransferases, the test for this marker is not yet widely available. For the present, it is best to rely on standard LFT results as biological markers for alcohol intake. In addition, providers can use periodic random Breathalyzer[™] tests to monitor alcohol intake and to provide positive feedback to patients who are successful in maintaining abstinence.

Markedly diminished craving. Craving that has diminished greatly is an optimum outcome of naltrexone treatment. To assess craving, the patient's own subjective reports can be largely relied on, although objective measures may also prove useful. More important than the method of monitoring is consistency in how the patient is asked about craving patterns and trends. Assessment of craving is most useful within the context of specific time frames. Patients should be asked about craving at the present time as well as how they have been feeling over the past week. It may be useful to ask them to rate their most intense episode of craving and whether any episodes of craving have caused

particular problems for them. The pattern of craving over time is a more telling indicator than an absolute number on a scale. In this way, both the provider and the patient can see that the patient's patterns of craving may be fluctuating throughout the day and over longer periods, which can provide a more accurate assessment of the appropriateness to continue, adjust, or terminate naltrexone treatment. Self-report instruments have been developed to assess craving. Examples include the Alcohol Urge Questionnaire (Bohn et al., 1995), which has the advantage of being short and easy to administer, and the Obsessive Compulsive Drinking Scale (Anton et al., 1996). These instruments are presented in Appendix D. It is important to educate the patient about the role of craving in relapse.

Improvement in quality of life. Ultimately, one of the goals of treatment is improved quality of life. In this regard, it is important to identify changes over time and to view the goal as being an improvement, rather than a total elimination, of problems. Areas to be assessed should include

- Health:
 - o Blood pressure, previously elevated, returns toward normal
 - LFT results show improvement
 - Stabilization occurs for other related medical problems that the patient was experiencing when he or she began treatment (such as control of blood glucose, stabilization of asthma, cardiomyopathy, encephalopathy, or ascites and edema)
 - Signs of increased engagement in general health care, such as seeing a physician for the first time in years and/or increased compliance with prescribed medication regimens other than naltrexone (e.g., asthma or blood pressure medications)
- Family:
 - Spending more positive time with children and/or spouse
 - o Greater involvement/participation with family members
 - Improved intimate relationships
 - Reduced family conflict (see TIP 25, Commented out Element*Substance Abuse Treatment and Domestic Violence*Commented out Element [CSAT, 1997], for issues concerning substance abuse and domestic violence)
- Work/vocational status:
 - Engagement in nondrinking leisure and recreational activities
 - Obtaining employment
 - o Improved attendance at work
 - Fewer job-related problems
 - Improved job performance
- Legal status:
 - No new parole or probation violations
 - No new driving-under-the-influence charges
- Mental status:
 - Decreased psychological symptoms
 - Decreased irritability and anxiety

- Improved mood
- Improved sleep
- Getting appropriate treatment for anxiety disorders, depression, or schizophrenia rather than self-medicating with alcohol

Abstinence from other substances of abuse. It is important to focus not just on alcohol use but also to address other substances of abuse that pose the same level of concern and possible adverse consequences. The abuse of other substances can be evaluated by random urinalysis, collateral reports from family or employer (with the patient's written consent), and self-reports from the patient. In addition to illicit substances, abuse of prescription and nonprescription medications is an important issue and should be addressed. In this regard, the patient's agreement or resistance to continuing treatment may indicate the level of willingness to consider the abuse of other substances as a problem.