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Naltrexone And Alcoholism Treatment
Treatment Improvement Protocol (TIP) Series 28

Stephanie O'Malley, Ph.D.
Consensus Panel Chair
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
Rockwall II, 5600 Fishers Lane
Rockville, MD 20857

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What Is a TIP?

Treatment Improvement Protocols (TIPs) are best practice guidelines for the treatment of substance abuse, provided as a service of the Substance Abuse and Mental Health Service Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT). CSAT's Office of Evaluation, Scientific Analysis and Synthesis draws on the experience and knowledge of clinical, research, and administrative experts to produce the TIPs, which are distributed to a growing number of facilities and individuals across the country. The audience for the TIPs is expanding beyond public and private substance abuse treatment facilities as alcohol and other substance abuse disorders are increasingly recognized as a major problem.

The TIPs Editorial Advisory Board, a distinguished group of substance abuse experts and professionals in such related fields as primary care, mental health, and social services, works with the State Alcohol and Other Drug Abuse Directors to generate topics for the TIPs based on the field's current needs for information and guidance.

After selecting a topic, CSAT invites staff from pertinent Federal agencies and national organizations to a Resource Panel that recommends specific areas of focus as well as resources that should be considered in developing the content of the TIP. Then recommendations are communicated to a Consensus Panel composed of non-Federal experts on the topic who have been nominated by their peers. This Panel participates in a series of discussions; the information and recommendations on which they reach consensus form the foundation of the TIP. The members of each Consensus Panel represent substance abuse treatment programs, hospitals, community health centers, counseling programs, criminal justice and child welfare agencies, and private practitioners. A Panel Chair (or Co-Chairs) ensures that the guidelines mirror the results of the group's collaboration.

A large and diverse group of experts closely reviews the draft document. Once the changes recommended by these field reviewers have been incorporated, the TIP is prepared for publication, in print and online. The TIPs can be accessed via the Internet on the National Library of Medicine's home page at the URL: http://text.nlm.nih.gov. The move to electronic media also means that the TIPs can be updated more easily so they continue to provide the field with state-of-the-art information.

Although each TIP strives to include an evidence base for the practices it recommends, CSAT recognizes that the field of substance abuse treatment is evolving, and published research frequently lags behind the innovations pioneered in the field. A major goal of each TIP is to convey "front-line" information quickly but responsibly. For this reason, recommendations proffered in the TIP are attributed to either Panelists' clinical experience or the literature. If there is research to support a particular approach, citations are provided.

This TIP, *Naltrexone and Alcoholism Treatment*, presents current knowledge about the use of naltrexone, an opioid antagonist medication first synthesized in the 1960s and subsequently developed by the National Institute on Drug Abuse (NIDA). This medicine was initially developed to treat opiate addiction. Subsequently, research sponsored by the National Institute on Alcohol Abuse and Alcoholism, which research is still ongoing, found that naltrexone can help prevent relapse to alcohol use disorder when combined with traditional treatment modalities. *Naltrexone, when combined with appropriate psychosocial interventions, relieves the craving for alcohol (and opiates) and decreases the relapse rate to heavy use*. Naltrexone has been proven safe for most adults except pregnant or nursing women, the very obese (at doses higher than herein recommended for daily use), and probably those with acute hepatitis; women of child-bearing potential must be tested monthly for pregnancy.

This TIP describes the medication itself, its mode of action, possible common adverse effects, and interactions with other medications. A separate chapter on the clinical use of naltrexone presents guidelines for selecting patients who may benefit from naltrexone and for starting and maintaining these patients on naltrexone. Issues for program managers and administrators, including staff education and procedures for getting new drugs on health care system formularies, are presented in appendixes.

As naltrexone is used more widely, alcohol treatment programs will continue to be a source of important data about its use, and this TIP offers suggestions for research in several areas. Funding for the study of treatment and outcomes is available periodically from NIDA, National Institute on Alcohol Abuse and Alcoholism, SAMHSA, and other Federal agencies.

This TIP represents another step by CSAT toward its goal of bringing national leadership to bear in the effort to improve substance abuse treatment in the United States.

Other TIPs may be ordered by contacting the National Clearinghouse for Alcohol and Drug Information (NCADI), (800) 729-6686 or (301) 468-2600; TDD (for hearing impaired), (800) 487-4889. TIPs are also available through the National Library of Medicine's home page at http://text.nlm.nih.gov.

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Baltimore, Maryland

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National Institute on Alcohol Abuse and Alcoholism

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Seattle, Washington

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Chairman

Division of Substance Abuse Medicine

Medical College of Virginia

Richmond, Virginia

Consensus Panel

Chair

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> Department of Psychiatry
> Yale University
> New Haven, Connecticut

Workgroup Leaders

Raymond Anton, M.D.
> Professor of Psychiatry
> Institute of Psychiatry
> Medical University of South Carolina
> Charleston, South Carolina

Mary Elizabeth McCaul, Ph.D.
> Associate Professor
> Department of Psychiatry and Behavioral Sciences
> School of Medicine
> Johns Hopkins University
> Baltimore, Maryland

Patrice Muchowski, Sc.D.
> Vice President
> Clinical Services
> Adcare Hospital of Worcester
> Worcester, Massachusetts

Robert Swift, M.D., Ph.D.
> Psychiatrist-In-Chief
> Department of Psychiatry
> Roger Williams Medical Center
> Providence, Rhode Island

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> Chief Executive Officer
> Administration
> SMARxT Consultants

Wilmington, Delaware

Ray Daw

Executive Director

Robert Wood Johnson Foundation

Northwest New Mexico Fighting Back, Inc.

Nanizhoozhi Center, Inc.

Gallup, New Mexico

Joseph Gallina, Pharm.D.

Director

Pharmacy Services

University of Maryland Medical System

Baltimore, Maryland

Hans C. Geisse, M.D.

Chief

Chemical Dependency and Recovery Program

Southern California Permanente Medical Group

Moreno Valley, California

Robert S. Geissinger

Counselor

Division of Alcoholism and Substance Abuse

Washington State Department of Social and Health Services

Lacey, Washington

Sarz Maxwell, M.D.

Program Coordinator

Center for Addictive Problems

Chicago, Illinois

David W. Oslin, M.D.

Assistant Professor

Addiction and Geriatric Psychiatry

Department of Psychiatry

University of Pennsylvania

Philadelphia, Pennsylvania

Special Consultants

Charles P. O'Brien, M.D., Ph.D.

Professor and Director

Treatment Research Center

University of Pennsylvania

Philadelphia, Pennsylvania

Robert Rosenheck, M.D.

Director

Division of Mental Health Services and Treatment Outcome Research

School of Medicine

Yale University

New Haven, Connecticut

Joseph Volpicelli, M.D., Ph.D.

Associate Professor

Treatment Research Center

University of Pennsylvania

Philadelphia, Pennsylvania

Foreword

The Treatment Improvement Protocol (TIP) series fulfills SAMHSA/ CSAT's mission to improve treatment of substance use disorders by providing best practices guidance to clinicians, program administrators, and payers. TIPs are the result of careful consideration of all relevant clinical and health services research findings, demonstration experience, and implementation requirements. A panel of non-Federal clinical researchers, clinicians, program administrators, and patient advocates debates and discusses their particular area of expertise until they reach a consensus on best practices. This panel's work is then reviewed and critiqued by field reviewers.

The talent, dedication, and hard work that TIPs panelists and reviewers bring to this highly participatory process have bridged the gap between the promise of research and the needs of practicing clinicians and administrators. We are grateful to all who have joined with us to contribute to advances in the substance abuse treatment field.

Nelba Chavez, Ph.D.

Administrator

Substance Abuse and Mental Health Services Administration

Camille T. Barry, Ph.D., R.N.

Acting Director

Center for Substance Abuse Treatment

Substance Abuse and Mental Health Services Administration

Executive Summary and Recommendations

Psychosocial treatments for alcoholism have been shown to increase abstinence rates and improve the quality of life for many alcoholics. Nonetheless, a significant proportion of alcoholics find it difficult to maintain initial treatment gains and eventually relapse to problematic drinking. Some of these individuals can now be helped with naltrexone, an opiate antagonist recently approved by the Food and Drug Administration (FDA) to treat alcohol abuse disorders. 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

This TIP will help clinicians and treatment providers use naltrexone safely and effectively to enhance patient care and improve treatment outcomes.

Naltrexone therapy improves treatment outcomes when added to other components of alcoholism treatment. For patients who are motivated to take the medication, naltrexone is an important and valuable tool. In many patients, a short regimen of naltrexone will provide a critical period of sobriety, during which the patient learns to stay sober without it.

The Consensus Panel that developed this Treatment Improvement Protocol (TIP) made recommendations based on a combination of clinical experience and research-based evidence. Their guidelines are summarized below. Those supported by the research literature are followed by (1); clinically based recommendations are marked (2). Citations to the former are referenced in the body of this document, where the guidelines are presented in full detail.

Concurrent Psychosocial Interventions

Naltrexone has been approved as an adjunct to psychosocial treatment and should not be seen as a replacement for psychosocial interventions. Treatment is significantly more successful when the patient is compliant with both the medication and psychosocial programs. Psychosocial treatments are likely to enhance compliance with pharmacotherapy, and likewise, pharmacotherapies enhance psychosocial treatment by reducing craving and helping the patient remain abstinent.

Pharmacological Management

Eligibility for Treatment

The following details some of the criteria for determining patients' eligibility for treatment with naltrexone:

- 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) are suitable candidates for naltrexone therapy.
- Individuals with acute hepatitis or liver failure are not suitable candidates.
- Patients requiring narcotic analgesia also are not suitable candidates.
- Appropriate candidates should 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.
- Patient interest and willingness to take naltrexone are important considerations.
- At the currently recommended dose of 50 mg daily, hepatic toxicity is very unlikely. Continued alcohol use is more likely than naltrexone to cause liver damage. Before determining a patient's eligibility for naltrexone therapy, clinicians should be aware that alcohol alone may be responsible for pretreatment elevated liver function test (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. (2) If the levels dramatically improve, then the patient may be a suitable candidate for naltrexone.
- Providers should perform LFTs prior to treatment initiation and periodically during treatment. The Consensus Panel recommends caution in using naltrexone with patients whose serum aminotransferases results are five times above normal. (1) 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. Patients with an elevation of total bilirubin should be referred to an internist or hepatologist for a consultation prior to considering naltrexone therapy.
- The final decision to use naltrexone should be based on a risk-benefit 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.

Naltrexone and Other Substances

The use of other substances during naltrexone treatment, particularly illegal opiates and opioid-containing medications, may pose the same level of concern and possible adverse consequences as the use of alcohol. Random urinalysis, collateral reports from family members or employer (with the patient's written consent), and self-reports from the patient can be used to evaluate the

use of other substances. In addition to illegal substances, the use of both prescription and nonprescription medications should also be addressed. 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.

Interactions with opiates and opioids

Because naltrexone may cause or worsen opiate withdrawal in subjects who are physiologically dependent on opiates or who are in active opiate withdrawal, it is contraindicated in these patients until after they have been abstinent from opiates for at least 5 to 10 days, or longer if they are withdrawing from methadone without benefit of buprenorphine (Buprenex) (once approved). (1) Naltrexone is absolutely contraindicated in patients currently maintained on methadone or LAAM (levo-alpha-acetyl-methadol) for the treatment of opiate dependence. (1) Naltrexone does not interfere with nonopioid pain medications such as ibuprofen, acetaminophen, and aspirin. (1)

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. (2)

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.

Interactions with other drugs

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) and oral hypoglycemics. The Consensus Panel recommends that clinicians be aware of all of the patient's medications and watch closely for naltrexone's interactions with other drugs. Clinicians should report adverse drug-drug interactions to the manufacturer(s) if they do occur. Concurrent use of antidepressants and naltrexone appears to be safe.

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. Patients on naltrexone are less likely to relapse to heavy drinking following a lapse in abstinence. However, both patient and provider should know that naltrexone does not make people "sober up" and does not alter alcohol's acute effects on cognitive functioning.

Starting Treatment

Patient education comes first

Patients must be taught how naltrexone works and what to expect while taking it. 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 returning to heavy drinking. Providers should negotiate a treatment plan with the patient at each stage of therapy.

Initial medical workup

The pretreatment medical workup should include

- A complete physical examination, including the liver
- Various laboratory tests, including LFTs (e.g., serum aminotransferases, total bilirubin)
- A pregnancy test
- A urine toxicology screen
- A complete/updated medical history to rule out possible contraindications
- A substance abuse history that focuses on the use of other substances, especially opiates, as well as the patient's history of use, misuse, or abuse of prescribed medications

- A mental health/psychiatric status screening

Positive mental health/psychiatric 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. (1)

Pretreatment abstinence

Naltrexone should be initiated after signs and symptoms of acute alcohol withdrawal have subsided. The Consensus Panel recommends that patients be abstinent for 3 to 7 days before initiating naltrexone treatment. (2)

Starting doses

The FDA has established guidelines for the dosage and administration of naltrexone. 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. Because adverse events may make the patient reluctant to continue the medication, the starting dose can be reduced for several days or divided in two. (2) 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.

Management of common adverse effects

Common adverse effects, which may include nausea, headache, dizziness, fatigue, nervousness, insomnia, vomiting, and anxiety, occur at the initiation of treatment in approximately 10 percent of patients. The Consensus Panel recommends the following strategies:

- **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.** The Consensus Panel recommends morning dosing for most patients to establish a routine and ensure better compliance. (1) Naltrexone should ideally be taken after the "regular" morning routine, preferably with food. Individual patient needs can also guide the timing of doses.
- **Split dosage.** If there is a need to split the dose, then the patient should take half in the morning and half in the evening, preferably with dinner.
- **Management of nausea.** Nausea is a problem for approximately 10 percent of patients and may reduce compliance. To minimize nausea, patients can take naltrexone with complex carbohydrates such as bagels or toast and not take the medication on an empty stomach. (2) The use of simethicone (e.g., Maalox) or bismuth subsalicylate (e.g., Pepto-Bismol) before taking naltrexone may help. 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. (2)
- **Withdrawal.** Patients may not be able to discriminate between the common effects of withdrawal from alcohol and the common adverse effects caused by naltrexone. Patients should be reassured that their symptoms will get better with time. Alcohol withdrawal can be managed with support or benzodiazepines if indicated.

Ongoing Treatment With Naltrexone

Maintenance doses

Low doses

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 daily dose may be divided in two and given at those times of the day when craving is strongest.

Higher doses

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 efficacious at these higher doses.

Before adjusting dosage, providers should first consider intensification of other treatment interventions, particularly psychosocial components. The reason the medication is not working should be explored. 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, 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, possible protocols are 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.

Duration of treatment

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. (2) 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. 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. (2) Factors to be weighed in the clinical decision to extend treatment beyond 3 to 6 months include patient interest, recent dose adjustment, partial treatment response, and prophylaxis in high-risk situations.

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 medication is added to the treatment, or symptomatology indicates the need for monitoring.

Pain management

Because naltrexone blocks the effects of usual doses of therapeutic opioids, providers should use nonnarcotic methods of analgesia as first line of treatment for pain conditions. If narcotic pain relief is indicated, patients must discontinue naltrexone use for the period during which analgesics are required. If a painful event such as surgery is anticipated, then naltrexone should be discontinued 72 hours prior to the procedure. (1) If a patient is taken off naltrexone and put on an opioid analgesic, he or she should be abstinent from the narcotic for at least 3 to 5 days before resuming naltrexone treatment. (1)

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. Respiratory assistance and support must be available, should this be necessary. The Consensus Panel recommends that patients on naltrexone always carry safety identification cards providing information that the patient is receiving naltrexone and instructions for treating patients in the event of an emergency.

Continued drinking

The continued or periodic drinking of alcohol may not be a sufficient reason to discontinue naltrexone: Some patients respond to naltrexone treatment at first by reducing rather than stopping their drinking. When a patient drinks during treatment, the treatment provider should evaluate whether the patient is taking his or her medication regularly and actively participating in treatment. The intensity of care along with the expectations placed on the patient may be increased. Dose adjustments may also be indicated.

Abstinence should be a desired goal for the patient; however, reductions in drinking may be an acceptable intermediate outcome. Failure to maintain complete abstinence is not necessarily a failure of treatment because there are many other areas of a patient's life that can improve, such as job performance, social relationships, and general physical health.

Use of naltrexone in conjunction with disulfiram

The concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks. If naltrexone is used with disulfiram, then treatment providers should perform LFTs shortly after the initiation of combined use. Providers should retest patients every 2 weeks for 1 to 2 months and thereafter at regular intervals, such as monthly. (2) Combination therapy with disulfiram and naltrexone should not be used for very long periods, and generally, the two drugs should not be started simultaneously.

Ending Naltrexone Therapy

Successful termination of naltrexone

Because naltrexone is not addicting, patients who stop taking the medication do not suffer from withdrawal symptoms, so naltrexone therapy can be discontinued without tapering the dose. Nonetheless, dose reductions may be psychologically useful to the patient. The treatment team should work with the patient in developing structured plans in the event of threatened or actual relapse. Scheduled followup visits ("booster visits") may also be helpful in providing support for the patient and opportunities for intervention based on identifying early signs of potential relapse. Naltrexone may be restarted if the patient and the treating clinicians feel that it may be helpful in preventing relapse.

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. Some of the possible criteria that can be used and selected to fit each program's needs and policies include

- Compliance with treatment plan
- Stable abstinence or significant reduction in the frequency and amount of drinking, as indicated by patient self-reports, collateral reports, and biological markers
- Markedly diminished craving
- Improvement in quality of life, including physical and mental health status, family and social relationships, work and/or vocational status, and legal status
- Abstinence from other substances of abuse

Other Topics

This TIP reviews 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 for providers who do not have a medical background explains how naltrexone works.

Also reviewed are the specific findings of the initial two clinical trials that established the efficacy of naltrexone in the treatment of alcohol dependence. This document describes the 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.

The TIP 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.

Appendix B guides clinicians and 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 Web sites for readers who may want to access additional information about substance abuse treatment through the Internet. Appendix C 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 about how to prepare the system for this change. Finally, Appendix D provides two instruments to help treatment providers who would like to monitor craving in their patients: The Obsessive Compulsive Drinking Scale and the Alcohol Urge Questionnaire.

This TIP will give treatment providers the information they need, first to determine which patients can benefit from naltrexone and second to safely and effectively administer the medication. Although research on the use of naltrexone for alcohol abuse disorders is ongoing, this TIP presents the "state of the art" from the country's leading experts on this important advance in substance abuse 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 (Institute for Health Policy, 1993; Institute of Medicine, 1996). 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 (Miller and Hester, 1986). 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. Appendix B 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. Appendix C 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. Appendix D 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., Gonzalez and Brogden, 1988; Sax et al., 1994) . 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 Chapter 5.)

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 risk-benefit 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*.)

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.

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.

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. Figure 2-3 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 (see PDR, 1997). 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 (Croop et al., 1997), 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 Chapter 5 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).*

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.

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.

Use of naltrexone in conjunction with disulfiram

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.

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(Annis and Peachy Peachey, 1992)and is currently being investigated for naltrexone(Kranzler et al., 1997).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--carbohydrate-deficient 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:*
  - 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
  - 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
  - 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.

Chapter 3 --Basic Neurobiological and Preclinical Research

Over the past decade, basic neurobiological research has enhanced our understanding of the biological and genetic causes of addiction. These discoveries have helped establish addiction as a biological brain disease that is chronic and relapsing in nature (Leshner, 1997). By mapping the neural pathways of pleasure and pain through the human central nervous system (which includes the spinal cord and brain), investigators are beginning to learn how abused psychoactive drugs, including alcohol, interact with various cells and chemicals in the brain. As scientists increase their knowledge, medications are being designed to reverse, control, or minimize the negative effects of substance abuse (Charness, 1990; Kuhar, 1991; National Institute on Alcohol Abuse and Alcoholism [NIAAA], 1994).

Fundamentals of the Nervous System

The human nervous system is an elaborately wired communication system that networks the entire body, and the brain is the central communications center of this system. The brain processes sensory information from throughout the body, guides muscle movement and locomotion, regulates a multitude of bodily functions, forms thoughts and feelings, and controls all behaviors. The fundamental functional unit of the nervous system is a specialized cell called a *neuron*, which conveys information both electrically and chemically. The function of the neuron is to transmit information: It receives signals from other neurons, integrates and interprets these signals and, in turn, transmits signals on to other, adjacent neurons (Charness, 1990).

A typical neuron (see Figure 3-1) consists of a main cell body (which contains the nucleus and all of the cell's genetic information), a large number of short-branched filaments called *dendrites*, and one long fiber known as the *axon*. At the end of the axon are additional filaments that form the connections with the dendrites of other neurons. Within neurons, the signals are carried in the form of electrical impulses. But when signals are sent from one neuron to another, they must cross a gap from one cell membrane to another. The gap at the point of connection between the neurons is called a *synapse*. At the synapse, the electrical signal within the neuron is converted to a chemical signal. The chemical messengers that transmit the signal are called *neurotransmitters*. Neurons communicate with other neurons by releasing neurotransmitters, which travel across the synapse and bind or adhere to specially formed receptors that are lodged on the outer surface of the target neuron (Charness, 1990). Approximately 50 to 100 different endogenous neurotransmitters, with one or many binding sites or receptors, have been identified in the human body. Figure 3-2 illustrates a typical synaptic connection and depicts the chemical communication mechanism. Neurotransmitters may have different effects depending on the subtype of receptor activated. Some increase a receiving neuron's responsiveness to an incoming signal--an excitatory effect--whereas others may diminish the responsiveness--an inhibitory effect. The responsiveness of individual neurons within the brain affects how the brain functions as a whole (how it integrates, interprets, and responds to information), which in turn affects the function of the body and the behavior of the individual. The accurate functioning of all neurotransmitter systems is essential to ensure normal brain activities (NIAAA, 1994; Hiller-Sturmh fel, 1995).

Neurological Reinforcement Systems And Drug Dependence

Psychologists have long recognized the importance of positive and negative reinforcement for learning and sustaining particular behaviors (Koob and LeMoal, 1997). Beginning in the late 1950s, scientists observed in animals that electrically stimulating certain areas of the brain led to changes in mental alertness and behavior. Rats and other laboratory animals could be taught to self-stimulate pleasure circuits in the brain until exhaustion. If cocaine, heroin, amphetamines, or nicotine were administered, for example, sensitivity to pleasurable responses was so enhanced that the animals would choose electrical stimulation of the pleasure centers in their brains over eating or other normally rewarding activities. The above process in which a pleasure-inducing action becomes repetitive is called positive reinforcement. Conversely, abrupt discontinuation of alcohol, opiates, and other psychoactive drugs following chronic use was found to result in discomfort and craving. The motivation to use a substance in order to avoid discomfort is called negative reinforcement. Positive reinforcement is believed to be controlled by various neurotransmitter systems, whereas negative reinforcement is believed to be the result of adaptations produced by chronic use within the same neurotransmitter systems.

Experimental evidence from both animal and human studies supports the theory that alcohol and other commonly abused drugs imitate, facilitate, or block the neurotransmitters involved in brain reinforcement systems (NIAAA, 1994). In fact, researchers have posited a common neural basis for the powerful rewarding effects of abused substances (for a review, see Restak, 1988). Natural reinforcers such as food, drink, and sex also activate reinforcement pathways in the brain, and it has been suggested that alcohol and other drugs act as chemical surrogates of the natural reinforcers. A key danger in this relationship, however, is that the pleasure produced by drugs of abuse can be more powerfully rewarding than that produced by natural reinforcers (NIAAA, 1996).

Unlike many other drugs of abuse (e.g., opiates, phencyclidine), alcohol does not interact with a specific receptor in the brain but appears to stimulate the release of many neurotransmitters (Koob et al., 1994). The development and persistence of alcohol dependence is a complicated process that is not yet completely understood. A number of lines of research are currently proceeding simultaneously to better understand the interaction between neurotransmitters and their receptors in encouraging drinking and the development of alcohol dependence (Froehlich, 1995). Investigations have recently confirmed that the key neurotransmitter systems that apparently interact with each other to mediate the reinforcing effects of alcohol include endogenous opioids, dopamine, serotonin, gamma-aminobutyric acid (also known as GABA), and the excitatory amino acid glutamate.

Alcohol and Neurotransmitters

Endogenous opioids, a class of neuropeptides that includes endorphins and enkephalins, produce euphoric, pleasurable effects such as "runner's high"; these neuropeptides also reduce sensitivity to pain. Heroin and morphine (which are called opiates; see Figure 3-3 for a comparison of opiates versus opioids) mimic the effects of endogenous opioids by stimulating opioid receptors. Alcohol also stimulates the release of endogenous opioids, which in turn activate the central

dopamine reward system (Koob et al., 1994; Froehlich, 1996, 1997).

Dopamine produces immediate feelings of pleasure and elation that reinforce such natural activities as sex and eating in both humans and animals and motivates the repetition of these activities. Dopamine is believed to play an important role in reinforcement and motivation for repetitive actions (Di Chiara, 1997; Wise, 1982). Alcohol appears to increase dopamine release in a dose-dependent manner; that is, more dopamine is released when higher doses of alcohol are given (Nash, 1997; Ulm et al., 1995). It is believed that alcohol stimulates dopamine release via both indirect mechanisms (gustatory stimuli) and direct actions on the brain and that alcohol-induced stimulation of dopaminergic pathways in the brain may be at least partially controlled by the endogenous opioid system (Di Chiara, 1997; Froehlich and Wand, 1996).

Serotonin is associated with the reinforcing effects of many abused drugs through its mood-regulating and anxiety-reducing effects. Low levels of serotonin are associated with depression and anxiety.

Both animal and human studies have shown that alcohol administration increases levels of serotonin (LeMarquand et al., 1994; McBride et al., 1993). Selective serotonin reuptake inhibitors (SSRIs), a class of medications that includes fluoxetine (Prozac), increase serotonin concentrations in the brain. SSRIs have shown some efficacy in decreasing alcohol intake in both animals and humans (Ulm et al., 1995) and have shown some promise in treating alcohol-dependent adults (Naranjo et al., 1984, 1987, 1989, 1990). However, several small clinical trials have shown only modest effect of serotonergic agents in reducing alcohol consumption (Anton, 1995).

GABA is the primary inhibitory neurotransmitter in the central nervous system. Because alcohol intoxication is accompanied by the impaired coordination and sedation indicative of neuronal inhibition, researchers have investigated alcohol's effects on GABA and its receptors. The results of this research have shown that alcohol significantly alters GABA-mediated neurotransmission (for a review, see Mihic and Harris, 1997). $GABA_A$ (a subtype of GABA) receptors are also believed to mediate development of tolerance and dependence on alcohol. Alcohol is believed to exert its acute behavioral effects by a selective enhancement of $GABA_A$ receptor activity (Little, 1991). In support of this belief, $GABA_A$ receptor antagonists block the ability of alcohol to cause ataxia (inability to coordinate muscle activity during voluntary movement) and anesthesia (Frye and Breese, 1982; Liljequest and Engel, 1982). Alcohol also potentiates the effects of GABA in the cerebral cortex and cerebellum (Suzdak et al., 1986; Allan and Harris, 1987).

Glutamate, an excitatory neurotransmitter, is associated with many learning, memory, and developmental processes. Alcohol normally inhibits the effects of glutamate. However, during abstinence following chronic alcohol use, excitation of the glutamatergic system is believed to have a role in alcohol withdrawal-induced seizures (Gonzales and Jaworski, 1997).

In addition to affecting neurotransmitters, it appears that chronic use of alcohol may alter the structure and functioning of neurotransmitter receptors that have roles in intoxication, reinforcement, and dependence. Alcohol also may alter signal transduction, which is the process of converting messages from the signaling neuron into changes in the target neuron. *Alcohol dependence is also known to have a* genetic component involved in vulnerability to drug abuse and dependence. Studies have found that identical twins, who share a common genetic heritage, are more likely to share addictions than fraternal twins, who share only half their genes (Pickens et al., 1991). Similarly, men with alcoholic fathers are three to five times more likely than men without any familial history of alcoholism to experience early onset of alcoholism or other drug dependence (Goodwin et al., 1973; Cloninger, 1987, 1988). Laboratory animals can be bred to show a greater preference for alcohol, compared with other strains of the same species (Froehlich, 1995; NIAAA, 1994, 1996). A number of recent lines of research have been focused on examining differences in the genes, as well as endogenous levels of various neurotransmitters, in rodents and humans differing in genetic predisposition toward alcohol dependence.

Preclinical Research Linking Alcohol and Opioids

For more than 100 years, careful observers have noted that alcohol and opiates produce similar pharmacological effects of euphoria and sedation, even though these drugs have very different chemical structures. A certain degree of cross-tolerance between these drugs has been demonstrated in animals: Morphine will relieve alcohol-withdrawal symptoms in mice, whereas alcohol suppresses withdrawal symptoms in morphine-addicted rats (Volpicelli et al., 1991). A Sears catalog from the early 1900s reflects the same phenomenon in humans by advertising an opium-based treatment for alcoholism and a tincture of alcohol for relieving the opiate (laudanum) addiction that was common among women of that era. In the 1970s, addiction specialists

noted that opiate addicts would substitute alcohol for heroin when the latter was unavailable. In fact, opiates have often been described as a substitute drug for alcohol, and an increase in opiate availability has been reported to be accompanied by a decrease in alcohol drinking (for a review, see Siegel, 1986). Opiate addicts are known to increase alcohol consumption during withdrawal and decrease alcohol consumption during methadone treatment or when heroin or morphine is readily available and consistently used (Ulm et al., 1995; Volpicelli et al., 1991).

These observations and other research findings set the stage for more intensive preclinical investigations over the past 15 years into the links between alcohol consumption and both endogenous opioids and exogenous opiates. These studies found that

- Alcohol administration releases endogenous opioid peptides
- Important genetic differences exist in opioid response to alcohol consumption
- Opiate administration alters alcohol consumption
- Opioid receptor antagonists change alcohol consumption patterns

Alcohol's Effects on Release of Endogenous Opioids and Opioid Receptor Activity

For some time, scientists have suspected that alcohol stimulates release of endogenous opioids and affects opioid receptor activity. Alcohol consumption has been shown to stimulate the release of endorphins in both rodents and humans (Gianoulakis and Barcombe, 1987; Gianoulakis and Angelogianni, 1989; Gianoulakis et al., 1987, 1996; Thiagarajan et al., 1989) as well as in cell cultures of rat hypothalamus and pituitary (Gianoulakis and Barcombe, 1987; Gianoulakis et al., 1990; Keith et al., 1986). More recently, animal studies have also demonstrated that alcohol exposure also increases levels of another class of opioid peptides, the metenkephalins. Moreover, studies using rodents bred specifically for preference or nonpreference for alcohol and in humans with a positive or negative family history of alcoholism indicate that a genetic predisposition toward alcohol consumption is accompanied by alterations in the responsiveness of the endogenous opioid system (deWaele et al., 1992). Acute alcohol administration produces greater increases in release of endogenous opioids and larger increases in opioid peptide gene expression in alcohol-preferring rodents than in nonpreferring rodents (Froehlich, 1995; Froehlich and Wand, 1996). Acute alcohol administration has also been shown to increase endorphin and enkephalin gene expression and to increase opioid receptors in neuronal cell cultures (Charness et al., 1986, 1993; Jenab and Inturrisi, 1994; Li et al., 1996). Recently, Gianoulakis and colleagues found that individuals with a positive family history of alcoholism have lower baseline levels of β-endorphins than individuals with no family history of alcoholism (Gianoulakis et al., 1996).

Effects of Exogenous Opiate Administration and Withdrawal on Alcohol Consumption

A related line of research has explored the impact of exogenous opiates on alcohol consumption in animal models. Early studies found that rats injected with a single, high dose of morphine (30 mg/kg) decreased their alcohol consumption (Sinclair, 1974) and that this effect of morphine was dose dependent (Ho et al., 1976). These studies also reported that morphine administration did not alter water consumption, suggesting a selective effect of morphine on alcohol-drinking behavior (Sinclair, 1974). Self-administration of alcohol also increased if moderate to large doses of opioids were abruptly terminated and withdrawal symptoms precipitated (Volpicelli et al., 1991; O'Brien et al., 1996).

In contrast to these earlier findings, Reid and colleagues found that small doses of morphine (2.5 mg/kg) transiently increased the preference for alcohol in previously fluid-deprived rats when given limited (2-hour) access to alcohol or water immediately after injection (Reid et al., 1991). These results suggested that small doses of opiates or other pleasure-inducing drugs may have a priming effect in which small amounts of the rewarding substance increase the craving to consume more of the same substance. In contrast, if opioid receptors are already saturated by high levels of externally administered opioid agonists such as morphine or heroin, then drinking decreases.

Similarly, an addictive cycle (Figure 3-4) may be established in animals or humans as a result of consuming a small dose of alcohol, which like a small dose of morphine leads to modest increases in opioid receptor activity. Once opioid receptor activity has been primed, more alcohol is needed to ensure continued opioid receptor activity (Volpicelli et al., 1994). Therefore, a cycle may ensue during which the desire to increase or recapture feelings of pleasure or euphoria (particularly if withdrawal results in lower levels of the desired feeling) is translated into cravings for particular substances. The loss of control that follows the initial consumption of a reinforcing agent may provide the root mechanism for some, if not all, addictive behaviors.

Effects of Opioid Antagonists on Alcohol Consumption

Nonselective opioid antagonists like naloxone and naltrexone block opioid receptors and reverse the effects of endogenous opioid peptides as well as exogenous opiates (Froehlich, 1995; Swift, 1995). Studies conducted in both rodents and monkeys have demonstrated that naloxone and the longer acting naltrexone attenuate voluntary self-administration of alcohol and stress-induced increases in alcohol consumption, suggesting that these agents may prevent the reinforcing effects of alcohol consumption (Froehlich and Li, 1993; O'Brien et al., 1996). Pretreatment with opioid antagonists reverses most of the effects of endogenous opioids or exogenous opiates on alcohol preference. Two double-blind, placebo-controlled clinical trials on the effects of naltrexone on alcohol drinking in outpatient alcohol-dependent patients demonstrated that naltrexone can decrease the mean number of drinking days per week, the frequency of relapse, the alcohol-induced subjective "high," and the desire to drink (O'Malley et al., 1992; Volpicelli et al., 1992).

Chapter 4 --Clinical Findings

This chapter describes the two clinical trials that initially established the use of naltrexone as an effective adjunct to psychosocial therapy in the treatment of alcohol dependence. In addition, the chapter summarizes several newer trials of naltrexone in different clinical populations, briefly reviews other recent advances in pharmacotherapies for alcohol dependence, highlights some of the clinical variables associated with successful demonstrations of naltrexone's efficacy, and suggests directions for future research. A summary of the most relevant clinical findings with respect to naltrexone treatment concludes the chapter.

Initial Efficacy Studies

The efficacy of naltrexone treatment for alcohol dependence was initially demonstrated by two back-to-back studies conducted first at the Philadelphia Veterans Affairs (VA) Medical Center (Volpicelli et al., 1992) and subsequently at Yale University School of Medicine (O'Malley et al., 1992). Both research projects were 12-week, double-blind, placebo-controlled clinical trials that administered either 50 mg/day of naltrexone hydrochloride or identical-appearing placebo tablets with standardized psychosocial therapy or rehabilitation counseling in small outpatient samples. In the VA study, patients also participated in day hospital treatment for 1 month followed by twice weekly group therapy. The subjects in the Yale study received either supportive therapy or cognitive behavioral coping skills treatment once a week. The subjects were recently detoxified or abstinent for 1 week and met diagnostic criteria for alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders* (3rd edition, revised [DSM-III-R]; American Psychiatric Association, 1987). The study populations in both trials had no significant psychiatric illness or drug abuse problem other than alcohol.

The separate findings from both of these initial clinical trials were encouraging because they demonstrated the benefits of naltrexone as an adjunct to psychosocial therapy for the treatment of alcohol dependence (O'Malley et al., 1995). In fact, the findings were instrumental in the approval given by the Food and Drug Administration (FDA) in December 1994 to use naltrexone for this purpose--the first new medication approved by the FDA for treatment of alcohol dependence in nearly 50 years.

Three-Month Treatment Outcomes

The subjects who took naltrexone in the VA Medical Center study (Volpicelli et al., 1992) had significantly more favorable outcomes than those randomized to placebo in terms of decreasing the mean number of drinking days, relapsing to clinically significant drinking, and experiencing less craving for alcohol (see Figure 4-1). Many of the subjects in both groups were nonabstinent during the study (57 percent of the placebo cohort and 46 percent of the naltrexone group). However, naltrexone-treated subjects drank on an average of 1.6 percent of study days compared with 8.3 percent of study days for the placebo group. Only 23 percent of the naltrexone-treated subjects met criteria for relapse to heavy drinking (five or more drinks on an occasion, drinking on 5 or more days in a week, or coming to a study appointment with a blood alcohol concentration level above 100 mg/dl), whereas 54 percent of the placebo-treated subjects relapsed.

The most impressive effect of naltrexone, however, was seen in patients who did imbibe: Only 8 of 16 naltrexone-treated subjects (50 percent) went on to a full-scale relapse after sampling alcohol compared with 19 of 20 placebo-treated subjects (95 percent). Mean alcohol craving scores, which declined gradually over the course of the study in both groups, were significantly lower at termination for the naltrexone group compared with the placebo group in a covariate analysis taking baseline craving into account. Craving in this study was assessed by simply asking the subjects to rate their craving from 0 to 9, where 0 was equivalent to no craving and 9 was craving so severe that the subject was unable to resist a drink.

The results of the Yale study confirmed and extended those from the first trial by Volpicelli and colleagues in finding naltrexone superior to placebo on measures of abstention, relapse,

numbers of drinking days, amounts of alcohol consumed, and severity of alcohol-related and employment problems (O'Malley et al., 1992). Subjects who took naltrexone reported drinking on half as many study days (4.3 percent) as placebo-treated subjects (9.9 percent). Moreover, the naltrexone-treated subjects, who averaged 13.7 drinks during the trial, consumed only one-third as many standard drinks as the placebo-treated controls, who averaged 38 drinks. This difference was even greater between the naltrexone-treated subjects who completed the study--who averaged 12 drinks during the 12-week study--and those placebo-using subjects who remained in the study but averaged 44 drinks over the 3-month period.

To further explore the links between the two independent clinical trials that had slightly different subject populations and rehabilitation approaches, a combined analysis of the data from both studies was performed (O'Malley et al., 1995). The results for a total of 186 subjects in the combined samples (93 naltrexone- and 93 placebo-treated) validated the original findings. The naltrexone-treated group had higher rates of abstinence and significantly fewer relapses to heavy drinking than did the placebo cohort, particularly among the subset of subjects who did resort to alcohol consumption during the 3-month trials. Placebo-treated subjects were nearly twice as likely (1.87 times) as those receiving naltrexone to "slip" and, if they began to drink, they were also twice as likely (1.92 times) as those not on active medication to have an episode of heavy drinking. The naltrexone-treated group also drank on fewer days throughout the studies than did subjects who received placebo.

Six-Month Followup Results

O'Malley and colleagues followed up 80 of the original 97 patients from the Yale trial 6 months after discontinuation of treatment to determine whether naltrexone in combination with either supportive or coping skills therapy improved long-term outcomes (O'Malley et al., 1996a). At followup, subjects in the naltrexone-treated group had lower overall relapse rates and were less likely to meet diagnostic criteria for alcohol abuse or dependence, as measured by the alcohol section of the Structured Clinical Interview for DSM-III-R (SCID), than were the subjects who had received placebo. However, the positive effect of naltrexone on abstinence rates only persisted for the first month following termination of medication, and its impact on relapse prevention declined over time. Moreover, by the end of the sixth month, the subjects who had received placebo/coping skills therapy had improved rates of drinking and relapse that were similar to those of both naltrexone-treated groups. The investigators speculated that the effects of coping skills/relapse prevention training, even without medication, take time to emerge but contribute to positive long-term outcomes by providing specific tools and reinforcing a reliance on personal resources after treatment cessation. They also noted that abstinence during treatment was a strong predictor of sustained improvement.

Predictors of Treatment Response

Further explorations of the data from the two original clinical trials (O'Malley et al., 1992; Volpicelli et al., 1992) have attempted to specify the characteristics of subjects most responsive to naltrexone and the baseline variables that predict continued alcohol consumption despite psychosocial treatments. One purpose of such analyses has been to assist in the matching of patients to the most appropriate treatments. These studies (Volpicelli et al., 1995a; Jaffe et al., 1996) suggest that patients with high levels of alcohol craving or poor cognitive abilities tend to benefit greatly from naltrexone therapy.

Recent Studies in Subjects With Alcohol Dependence

Since the results of the original trials of naltrexone were published in 1992, several new studies have been completed and preliminary results published or presented. Two of these investigations highlight the importance of medication compliance to the efficacy of naltrexone (Volpicelli et al., 1997; Croop and Chick, 1996). Volpicelli and colleagues conducted a 12-week study of 97 alcohol-dependent and recently detoxified patients at the University of Pennsylvania/VA Treatment Research Center who were randomized to placebo or naltrexone along with individual therapy. Therapy focused on relapse prevention and occurred twice a week for the first month, tapering to weekly sessions in the second and third months (Volpicelli et al., 1997). Although most of the procedures were the same as those in the original VA Medical Center study of male veterans (Volpicelli et al., 1992), the patient population in this study was more heterogeneous, with a broader mix of ethnicities, more women (approximately 25 percent), and more married participants. The psychosocial treatment also was less intensive. Unlike the findings from the original clinical trials, however, naltrexone was not impressively superior to placebo in preventing relapse to heavy drinking. Although only one-third of the total naltrexone-treated group (35.4 percent) relapsed during the study compared with more than half of the total placebo sample (53 percent), these differences were not statistically different.

The results of the 1997 study did more clearly favor naltrexone over placebo among subjects who cooperated fully with the study protocol, missing no more than two research sessions (Volpicelli et al., 1997). Only one-fourth (25.7 percent) of the 35 naltrexone-treated subjects who completed the study experienced a relapse compared with more than half (52.8 percent) of their counterpart treatment completers in the placebo group. Naltrexone-treated patients who completed treatment also reported less than half the number of drinking days (5.4 percent) than did those who received placebo (12.7 percent) and were more likely to remain continuously abstinent (64 percent vs. 35 percent). The investigators concluded that the benefits of naltrexone in

reducing relapse to heavy drinking rely heavily on subjects' attendance and medication compliance. Consistent with this conclusion, the preliminary results of a double-blind placebo-controlled study of naltrexone conducted in the United Kingdom also found that naltrexone was superior to placebo only in the subset of patients who completed the 12-week trial and took 80 percent of their study medication (Croop and Chick, 1996). Thus, if the beneficial effects of this medication are to be fully realized, outpatient programs will need to incorporate naltrexone into a structured psychosocial treatment approach that facilitates both types of compliance.

Anton (1997) recently reported findings that more consistently favored naltrexone over placebo. The preliminary results of this study of 131 mild-to-moderately severe outpatient alcoholics who were relatively treatment-na ve indicated that naltrexone when combined with cognitive behavioral therapy (CBT) increased the nonrelapse rate from 40 percent in the placebo-treated group to 62 percent. In addition the percentage of days drinking and drinks per drinking day were also significantly decreased by naltrexone. Interestingly, the time between the first relapse drinking day (defined as five or more drinks per day for men and four or more drinks per day for women) and the second relapse drinking day was almost double for those treated with naltrexone and CBT compared with those receiving CBT alone. Naltrexone also allowed subjects to experience greater control and resistance over their thoughts about drinking and their urge to drink. Side effects of nausea, abdominal discomfort, daytime sedation, and nasal congestion were all experienced more frequently by the naltrexone-treated patients compared with placebo-treated patients.

Naltrexone was well tolerated by most patients: No one terminated due to adverse effects, and liver function normalized in a similar fashion in both the naltrexone- and placebo-treated groups. The results of this study, in which the patients had high treatment completion (83 percent) and medication compliance (70 percent), support the initial findings of the two 1992 studies (O'Malley et al., 1992; Volpicelli et al., 1992). It indicates that naltrexone can augment a highly useful psychosocial intervention in the outpatient treatment of alcoholism.

The average age of subjects participating in most studies of naltrexone is in the early forties. However, the population of older adults in the United States is increasing rapidly, and although little is known about the use of naltrexone with this population, many older alcohol-dependent individuals may be potential candidates for this medication. To address the efficacy of naltrexone in older alcoholics, Oslin and colleagues (Oslin et al., 1997) conducted a 12-week double-blind placebo-controlled study of male veterans, 50 to 70 years of age. Nursing staff administered the naltrexone to ensure compliance, giving subjects 100 mg each on Monday and Wednesday and 150 mg on Friday, using procedures similar to those used for opiate addicts taking naltrexone. Naltrexone was well tolerated by subjects, and they completed nearly 10 of the 12 weeks on average. Because of the small sample size, **the differences between the groups could not be considered statistically significant, though there were observable trends**. Specifically, 14.3 percent of those in the naltrexone-treated group relapsed, compared with 34.8 percent of those in the placebo-treated group ($p = .117$). However, among those who sampled alcohol, only three of the six subjects in the naltrexone-treated group subsequently relapsed, compared with all eight subjects who drank in the placebo group. Although the sample does not represent the oldest of the old, the study suggests that naltrexone is a viable treatment option for older adults.

Naltrexone Treatment For Other Patient Populations

Several studies have recently been completed, and more have been funded to investigate the efficacy of this approach with a variety of other patient populations, using different dosing levels and schedules, therapy combinations, treatment intensities, and time in care.

Cocaine and Alcohol Abuse

Concurrent cocaine abuse by alcohol-dependent persons is a more common problem than any other drug-alcohol combination, according to recent Epidemiologic Catchment Area (ECA) data (Regier et al., 1990). Drug-abusing alcoholic patients also have poorer treatment prognoses than individuals who only drink to excess. In an attempt to ascertain effective treatments for this comorbidity, Carroll and colleagues randomly assigned 18 outpatients meeting DSM-III-R criteria for cocaine and alcohol dependence but no other psychological disorder to either disulfiram (250 mg/day) or naltrexone (50 mg/day) together with weekly psychotherapy sessions over 12 weeks (Carroll et al., 1993). Although the investigators hypothesized that naltrexone would be associated with reductions in alcohol use comparable to those of disulfiram and also have a positive impact on cocaine use, disulfiram was found to be significantly more effective than naltrexone in reducing the frequency and quantity of alcohol use during treatment. Parallel but lesser reductions in cocaine use were also found among the subjects receiving disulfiram compared with those treated with naltrexone. Although the sample size was small and attrition was high in both groups (only four of nine subjects in the disulfiram group and two of nine in the naltrexone group completed all 12 weeks of treatment), the findings from this pilot study are disappointing with respect to naltrexone's lack of apparent efficacy as an adjunctive pharmacotherapy for patients with comorbid alcohol and cocaine problems.

A larger study of 109 alcoholics of whom approximately two-thirds had concomitant cocaine or opioid dependence found that over the course of a 6-month medication period, naltrexone was not significantly better than placebo in reducing alcohol consumption and relapse drinking (McCaul, 1996). However, early in the medication period (first and second months), individuals treated with naltrexone 100 mg did significantly better than the individuals treated with either naltrexone 50 mg or placebo. Furthermore, there was evidence that patients who had high blood

levels of naltrexone's active major metabolite did significantly better than patients with low blood levels. A recent open-label study of naltrexone (150 mg/day) in alcohol- and cocaine-dependent adults did show dramatic reductions in both alcohol and cocaine use (Oslin et al., 1997). Thus, higher doses of naltrexone may be beneficial in this select population. Additional trials at this higher dose are currently being conducted.

Heavy Drinkers

A 1994 study randomized 14 heavy drinkers who met DSM-III-R criteria for alcohol abuse or mild dependence (having no more than three of the nine dependence criteria) to 6 weeks of brief counseling (a 30-minute session in week 1, followed by 10-minute "booster" sessions in weeks 2, 3, 4, and 6) and either 25 mg/day or 50 mg/day of naltrexone (Bohn et al., 1994). Assessments were conducted during treatment, at termination, and after a 1-month followup period. Total alcohol consumption decreased in both dosage groups during the treatment period (63 percent from baseline) and over the entire course of monitoring (48 percent). The intensity of drinking, frequency of heavy drinking (a minimum of six drinks a day), craving for alcohol, and indicator values of liver function tests also declined for both groups during treatment; and subjects maintained these improvements for the 1-month posttreatment period.

Researchers also have investigated the potential utility of naltrexone on a targeted or "as needed" basis in an open-label study of 21 individuals who had a diagnosis of alcohol abuse or mild alcohol dependence and who drank more than 14 drinks per week for women and more than 20 drinks per week for men (Kranzler et al., 1997). Subjects were provided with four sessions of skills training and five naltrexone tablets each week. They were instructed to take at least two per week and to use the others as needed. During the treatment period, significant improvements were observed on a range of drinking-related outcomes. These measures included frequency of drinking, amount consumed per drinking day, number of drinking days, gamma-glutamyl transpeptidase (GGTP) levels, alcohol problem severity, and craving. Over the course of the 3-month posttreatment followup, significant improvements were still apparent for several measures, including frequency of drinking, GGTP levels, drinks per drinking day, and the number of heavy drinking days.

Although the sample size in these two studies was small and there was no placebo control group, the results suggest that it is feasible to use naltrexone in heavy drinkers and those with milder alcohol-related problems who may present in primary care settings. Placebo-controlled double-blind studies are currently under way to follow up on these promising findings. Preliminary analyses of a study in which open-label naltrexone was provided in conjunction with a primary care model of counseling to alcohol-dependent subjects also indicated that patients were generally satisfied with this model of care and improved significantly on a range of clinical outcomes (O'Connor et al., 1997).

Alcohol-Dependent Patients With Comorbid Psychiatric Diagnoses

Given that alcoholism is often associated with other psychiatric disorders, investigators are beginning to describe the use of naltrexone to augment the treatment response of the subset of alcohol-dependent patients with comorbid psychiatric diagnoses. Researchers reported that 82 percent of a sample of 72 dually diagnosed patients had at least a 75 percent reduction in drinking when treated clinically with 50 mg of naltrexone (Maxwell and Shinderman, 1997 [see Case Study 1 in Appendix C]). A recent small open-label study examined the effect of naltrexone on alcohol use and depressive symptoms among 14 depressed alcoholics who were continuing to drink despite selective serotonin reuptake inhibitor (SSRI) therapy for depression (Salloum et al., 1998). Encouragingly, the introduction of naltrexone to their therapeutic regime was associated with significant reductions in craving and drinking and mild improvement in depressive symptoms. The combination of naltrexone and antidepressant therapy also appears to be safe based on the results of the large-scale multisite trial in which nearly one-third of the patients were receiving concurrent antidepressant therapy (almost all were taking SSRIs) (Croop et al., 1995, 1997). Larger controlled studies are needed to conclusively evaluate the potential effectiveness of naltrexone in dually diagnosed patients.

Differential Subjective Effects of Naltrexone

Clinical Studies

Additional analyses of data obtained from the initial clinical trials of naltrexone examined the subjective effects experienced while drinking alcohol among subjects who did not remain abstinent throughout the studies (Volpicelli et al., 1995b). Of the 70 subjects in the original VA study, 36 met this criterion (Volpicelli et al., 1992). A larger proportion of these naltrexone-treated subjects (7 of 12) than placebo-treated subjects (2 of 17) reported that the "high" produced by drinking alcohol was significantly less than usual. The naltrexone-treated patients also drank less alcohol than the placebo-treated subjects during the first drinking episode--with only 17 percent of the naltrexone group meeting relapse criteria during the initial slip compared with 65 percent of the placebo group. There was no difference between groups in reported intoxication, loss of physical coordination, levels of alcohol craving, memory disturbance, or loss of temper. Volpicelli and colleagues speculated that these results reflect the blockade effects of naltrexone on opioid receptor activity with consequent loss of reinforcing

pleasurable stimulation, although an alternative explanation might be the lower levels of alcohol consumed by the naltrexone-treated subjects during their slips (Volpicelli et al., 1995b).

A similar reexamination of data from the original Yale study (O'Malley et al., 1992) revealed differences between subjects in the naltrexone- and placebo-treated groups with respect to their retrospective recollections of subjective reactions to alcohol effects and reasons for terminating an initial drinking episode (O'Malley et al., 1996b). Although the mean number of drinks consumed during the initial drinking episode did not differ greatly, the proportion of subjects who met relapse criteria was significantly lower for naltrexone-treated subjects (50 percent) than for placebo-treated subjects (81 percent). The 16 patients on naltrexone who did sample alcohol reported lower levels of intoxication and lower levels of craving before, during, and after their drinking episode than did their placebo-treated counterparts. Furthermore, the two groups offered different reasons for stopping drinking: The naltrexone-treated subjects were more likely to report reduced incentives for drinking (e.g., lower craving), whereas the placebo-treated subjects emphasized various adverse consequences of drinking as reasons for their stopping. The groups did not differ significantly in their ratings of the pleasure associated with the experience. The investigators concluded that the findings are consistent with naltrexone's hypothesized effects on modifying alcohol craving and the urge to drink among alcohol-dependent persons.

Laboratory Studies

Several other laboratory studies have investigated naltrexone's effects on subjective responses to drinking. Swift and colleagues used a double-blind, cross-over design to determine whether pretreatment with 50 mg of naltrexone affected a subsequent intoxicating dose of alcohol given to 19 nonalcoholic subjects (Swift et al., 1994). The results indicate that subjects reported feeling more sedated and less stimulated during the experiment on the day that they received naltrexone compared with the day that they received placebo naltrexone. Naltrexone pretreatment did not alter psychomotor performance or ethanol pharmacokinetics. Subjects pretreated with naltrexone also had more episodes of nausea and vomiting after the intoxicating dose of alcohol was administered, suggesting that these aversive effects may also decrease the desire to drink again. Given that nausea was not assessed prior to alcohol ingestion, however, the results do not clearly demonstrate whether the nausea was an adverse effect of naltrexone alone or the result of an interaction between naltrexone and alcohol. In fact, some dysphoria has been reported by detoxified opiate addicts treated with naltrexone (Gonzalez and Brogden, 1988). In direct contrast to the findings by Swift and colleagues, a subsequent study found that pretreatment with naltrexone did not significantly alter subjective responses to alcohol among light social drinkers (Doty and deWit, 1995).

A more recent study of the effects of naltrexone on drinking behavior found that naltrexone increased the time to the first sip for the first and the second drink in social drinkers who were observed in a bar setting over the course of 3 hours (Davidson et al., 1996). In addition, blood alcohol levels were lower on the day that subjects received naltrexone compared with the day that they received placebo naltrexone, confirming observed differences in drinking behavior.

King and colleagues noted that the euphoric effects reported by clinical samples of alcoholics after drinking may not be the same as those experienced by ordinary social drinkers (King et al., 1997). Pursuing previously observed differences in physiological responses to alcohol between subjects who are genetically at high or low risk for the development of alcoholism (Gianoulakis et al., 1990), these researchers examined the effect of naltrexone in these two groups on self-reported stimulation and sedation from alcohol as well as general mood states during rising and falling phases of intoxication as measured by breath alcohol levels (BALs). This comparison of 15 high-risk males with alcoholic fathers and 14 low-risk subjects--with no alcoholic relatives in two generations--confirmed the hypothesis that pretreatment with naltrexone would decrease the subjective stimulation (euphoria) experienced during the rising BAL phase immediately after alcohol consumption in the high-risk social drinkers compared with low-risk counterparts. The finding supports other research reports in humans and animals that opioid receptor antagonists decrease the reinforcing effect of drinking, especially among those who are at genetic risk for developing alcohol dependence. High-risk subjects in this study were also more likely than low-risk participants to correctly distinguish the naltrexone- from the placebo-influenced drinking sessions, reporting that alcohol effects achieved after receiving the placebo were more like everyday drinking. No significant naltrexone-related sedation effects during falling BALs were noted in either high- or low-risk groups, but more high-risk (four) than low-risk (one) subjects vomited during or shortly after the naltrexone session. The results of the King study suggest that such aversive effects of drinking after naltrexone pretreatment should not be overlooked, even though they were not statistically significant.

Naltrexone in the Context of Other Pharmacotherapies

Extensive recent research has focused on identifying and testing a variety of drugs to alleviate acute withdrawal symptoms among alcohol-dependent patients, rapidly induce sobriety or prevent intoxication, reduce alcohol craving and consumption, and ameliorate concurrent psychopathology or simultaneous dependence on illicit drugs. These advances in medications development over the past 5 years, which reflect neurobiological findings underlying drinking behavior, are cogently presented in a recent review (Litten et al., 1996); some of the most relevant findings are briefly summarized here regarding medications that are currently available or likely to be available in the near future. Essentially, researchers now concur that alcohol consumption is influenced by interactions among several neurotransmitter systems (e.g., opioid, gamma-aminobutyric acid [GABA], serotonin, dopamine, glutamate) as well as hormonal systems.

Other Opioid Antagonists

In addition to studies of naltrexone, investigators are examining the efficacy--in reducing the frequency and amount of alcohol consumption as well as relapse rates--of other opioid antagonists that have a strong affinity for particular opioid receptor subtypes. Human studies with nalmefene, an antagonist with particular affinity for &wingo; and &greekk; opioid receptors and less potential liver toxicity than naltrexone, have been particularly promising (Litten et al., 1996; Mason, 1996; Mason et al., 1994). Animal studies using naltrindole (a &wingo; opioid receptor antagonist) and naltriben (a &wingo;$_2$ opioid receptor antagonist) are also encouraging.

Acamprosate

Acamprosate (calcium acetylhomotaurinate) is a synthetic derivative of homotaurine, a structural analogue of GABA, which has yielded promising results in several European clinical trials with respect to decreases in drinking and increases in continuous abstinence or abstemious periods compared with placebo (for a review, see Wilde and Wagstaff, 1997). Acamprosate appears to be generally safe and has been shown to have a dose-response effect on drinking behavior. Treatment duration has varied between 3 and 12 months. A multisite clinical trial to test the efficacy and safety of acamprosate is currently being conducted in the United States.

Selective Serotonin Reuptake Inhibitors

Although the results of animal studies of SSRIs (e.g., fluoxetine [Prozac]) indicate that this type of medication reduces drinking, the effects among problem-drinking and alcohol-dependent humans have been far less impressive than those with naltrexone. The demonstrated antidepressant effects of SSRIs do, however, help in treating comorbid depression among alcoholics (Kranzler et al., 1995; Cornelius et al., 1997). In view of the sharply increasing use of SSRIs to treat a multitude of disorders, additional research is needed on the interaction between naltrexone and SSRIs in substance abuse treatment. The results of two preclinical studies suggest that agents that alter serotonin function may have some benefit in combination with naltrexone (Le and Sellers, 1994; Zink et al., 1997). Recent preliminary small-sample open-label studies tentatively suggest that the combination of antidepressant medications and naltrexone may be useful in reducing drinking in depressed (Salloum et al., 1998) and nondepressed alcohol-dependent patients (Farren and O'Malley, 1997). A larger placebo-controlled trial of the use of the SSRI sertraline to augment the efficacy of naltrexone in nondepressed alcohol-dependent patients is currently underway.

Serotonin Antagonists/Agonists

Laboratory studies and brief clinical trials of serotonin (5-HT3 and 5-HT2) antagonists have proved mostly disappointing, although animal models suggest that these antagonists suppress dopamine release in the mesocorticolimbic system and, by blocking reward systems, might decrease the desire to drink alcohol (LeMarquand et al., 1994; Pettinati, 1996). Some success has been achieved, however, by using the partial 5-HT1A agonist, buspirone, with patients diagnosed with alcohol abuse/dependence and collateral anxiety disorders (for a review, see Malec et al., 1996). When combined with cognitive behavioral therapy, this medication reduces anxiety symptoms and increases treatment retention. In addition, it appears to exert very modest effects on reducing the frequency of alcohol consumption and the risk of a return to heavy drinking in these patients (Kranzler and Meyer, 1989).

Tricyclic Antidepressants

Patients with coexisting alcohol dependence and depression have been treated with the tricyclic antidepressants desipramine and imipramine with modest-to-good results in terms of improved mood and reduced risk of relapse (McGrath et al., 1996; Mason et al., 1996). Both antidepressants significantly improved depression and to a certain extent also reduced drinking behavior.

Directions for Future Research

Both the literature and experience from clinical trials suggest that key areas for additional research on naltrexone treatment are

- Determining optimal dosing regimens with consideration for patient acceptance, common adverse effects, efficacy, and costs
- Determining the most effective initial duration of adjunctive naltrexone treatment and the conditions for extending or resuming use
- Evaluating the cost-effectiveness of naltrexone treatment

- Exploring the feasibility and acceptability of inpatient naltrexone induction to prevent relapse immediately after detoxification and to determine the potential for increased efficacy
- Identifying "responder" subpopulations whose characteristics (e.g., severity of alcohol-related problems, comorbid psychopathology or drug dependence, cognitive impairment, familial history of alcoholism, reported craving, demographics, general health) predispose them to successful, adjunctive use of naltrexone either alone or in combination with other pharmacotherapies
- Determining necessity for abstinence prior to initiating naltrexone or the feasibility of using this drug to help patients gradually reduce their drinking with the goal of abstinence
- Determining the effect of naltrexone in alcohol withdrawal
- Ascertaining the optimal psychosocial therapies (e.g., coping skills training, supportive therapy, cue extinction) and the intensity and duration with which they need to be applied for different patient subpopulations receiving adjunctive naltrexone
- Ascertaining the drug's effects on both the mother and fetus during pregnancy, on lactation in the new mother, and on the breast-feeding infant
- Researching the use of naltrexone with adolescent and elderly populations
- Ascertaining the efficacy of naltrexone in other clinical populations, including alcoholics in the criminal justice system, social drinkers with health problems, and heavy drinkers
- Determining the effectiveness of naltrexone in general populations of individuals with alcohol dependence
- Conducting followup studies of treated populations to determine drinking-related outcomes at different intervals following termination of medication
- Identifying effective strategies for enhancing compliance with medication administration, including the reduction of adverse effects, involving collaterals and other monitoring systems in assuring that medicine is taken as prescribed, and changing dosing regimens or developing depot formulations
- Exploring the efficacy of other opioid receptor-specific antagonists (e.g., nalmefene)
- Determining the biological mechanisms of alcohol's effects on endogenous opioids, the role of the opioidergic/dopaminergic reward system in alcoholism, and the relationships among several neurotransmitter systems that apparently influence drinking behavior
- Determining the mechanisms responsible for reductions in drinking behavior over time (e.g., craving, protracted withdrawal symptoms)
- Exploring combining naltrexone with other medications, such as selective serotonin reuptake inhibitors, disulfiram, and acamprosate

Summary

To date, most of the clinical studies of naltrexone as an adjunct to a broad spectrum of psychosocial therapies for alcohol-dependent or alcohol-abusing patient populations in brief-to-intensive structured treatment programs have demonstrated the superiority of this medication over placebo for reducing

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

Naltrexone also appears to significantly reduce the euphoric high experienced by alcohol-dependent drinkers and social drinkers who are at risk for becoming dependent because of their familial history of alcoholism. The effect of naltrexone on reducing the reinforcing properties of alcohol may help break the addictive drinking cycle in which one drink leads to another. Over the 6 months after treatment, patients who received naltrexone still have somewhat better outcomes than those given placebo with respect to overall relapse rates and drinking-related problems, although the positive effects of the medication seem to diminish after termination. However, many clients who continue to use the information and skills that they obtained and/or developed during treatment can and do stay sober. Compliance with the medication regimen and attendance at treatment sessions are both strong predictors of improved outcomes for populations treated with naltrexone.

Naltrexone's effect on decreasing alcohol craving is not as clear: The results of some studies indicate a significant reduction in this measure from baseline to termination compared with placebo, whereas others show few or inconsistent medication effects on the urge to drink, which is notoriously subjective and difficult to validate. Naltrexone, at a daily dose of 50 mg, does not appear to be efficacious in reducing alcohol and cocaine use among the sizable number of alcohol-dependent patients who simultaneously abuse cocaine. It may have, however, some efficacy among patients with other comorbid psychopathologies or at different dosage levels. A number of treatment-related issues need further exploration and resolution through additional research.

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-β-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-β-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-β-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-β-naltrexol, minor metabolites (e.g., 2-hydroxy-3-methoxy-6-β-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-β-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-β-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-β-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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Appendix B--Naltrexone and the Formulary

In many health care settings, naltrexone may not be on the formulary. This appendix provides substance abuse counselors and treatment providers who are interested in making naltrexone available for their patients with a greater understanding of the formulary system.

Introduction to the Formulary System

After a drug has been approved by the Food and Drug Administration (FDA) for treatment of a particular condition or disease, any licensed physician may prescribe it for that purpose, and any licensed pharmacist may dispense that prescription, on a patient-by-patient basis. Naltrexone hydrochloride, which was approved by the FDA in 1994 for use in the treatment of alcohol dependence, is thus theoretically available to any patient who demonstrates a need for it.

Within an integrated health care system, health maintenance organization (HMO), managed care organization (MCO), State substance abuse authority, or public health care system, however, the drug use process is more complicated. The number of FDA-approved medications is growing rapidly. The drugs themselves, as well as the ways in which they are administered, are often quite complex. Health care providers are concerned about the possibility of adverse reactions, side effects, and drug interactions. In addition, many new drugs are quite expensive, creating a need for pharmacoeconomic analyses. For these reasons, health care providers take measures to ensure that only those drugs with proven safety, efficacy, and cost-effectiveness are used within their organizations.

The *formulary* and the *formulary system* are tools that health care organizations use to improve the quality and control the cost of drug therapy (American Society of Hospital Pharmacists, 1991). A health care organization's pharmacy and therapeutics (P T) committee has a key role in maintaining the formulary system.

The *formulary* is a continually revised compilation of drug products that have been approved for use within a health care organization or system (American Society of Hospital Pharmacists, 1983). The formulary, for example, of a university-based health care system may include more than 3,000 products. Much more than an alphabetical product list, the formulary provides a wealth of information about each approved product, including generic and brand names, dosage form, strength, packaging, and size stocked by a pharmacy, as well as a list of active ingredients. The formulary entry for a particular product may also include indications for use, situations in which it should not be used (contraindications), drug interactions, and adverse drug reactions. The formulary also provides information regarding organizational policies and procedures concerning drug use and other special information.

Pharmacies do not stock products that are not on their formulary. If a physician prescribes such a drug, a pharmacist is responsible for discussing the request with the prescriber and determining whether an alternative formulary product can be used. At institutions such as the University of Maryland Medical System, where pharmacists work closely with physicians

on a day-to-day basis, more than 92 percent of such requests are resolved without recourse to a nonformulary product.

A *formulary system* is the process by which the medical staff of a health care organization, working through the P T committee, evaluates drug products and selects those it believes will be most beneficial in the care of patients for whom it is responsible (American Society of Hospital Pharmacists, 1983).

The P T committee is the "organizational keystone" to the formulary system (American Society of Hospital Pharmacists, 1992). Its members include physicians, pharmacists, and other health care professionals. The committee operates under the overall direction of the medical staff, and a pharmacist generally serves as its secretary. It formulates policies relating to drug evaluation, selection, procurement, storage, distribution, and use. The second major function of the P T committee is to develop or assist in developing training programs to educate staff members on issues related to drug use (American Society of Hospital Pharmacists, 1992).

How a Drug Is Added

The functioning of the formulary system, as well as the formulary itself, varies from setting to setting and from State to State. The process by which a drug is added to the formulary can best be characterized by examining three typical health care settings: a university-based health care system, an HMO or MCO system, and a State health care system. The following cases are meant to serve only as examples.

University-Based Health Care System Formularies

In this type of health care setting, the process of adding a drug to the formulary may entail the following steps.

Submission of a request

The process begins when a physician submits a written request form. The generic name of the drug is used in this request. (If the product is approved, the pharmacy will decide what brand to purchase.)

The written request asks for information about indications for use of the requested drug, products used for treating the condition of interest before the new product was available, and references from the peer-reviewed primary literature and combined analyses. The request also asks for anecdotal reports concerning the requestor's use of the product and for names of colleagues who may support the request. The form requests information about the principal diagnosis for which the medication will be used and the number of inpatients and outpatients expected to receive the drug each month. The pharmacy department uses this information to prepare budget forecasts.

Preparation of a drug monograph

Submission of a request triggers a review by the pharmacy's drug information service. The result of that review is *a drug formulary monograph.* This monograph, often prepared by a pharmacy doctoral candidate or a pharmacy resident, consolidates input from the requesting physician, the primary literature, and data that the pharmacy has requested from the drug's manufacturer. It often contains sections regarding indications, pharmacology (the drug's source, chemistry, and action), *pharmacokinetics* (how the drug moves through the body), efficacy, adverse effects, drug interactions, contraindications, administration route, dosage, monitoring, and cost. The monograph concludes with a recommendation for approval or rejection of the formulary request.

Data analysis

In the next step in the process, a pharmaco-economic analysis of the drug product is conducted. This analysis includes both therapeutic and fiscal factors. Figure B-1 presents a model of the formulary process at a major medical center. The model is especially valuable because it offers a structure through which concerns of clinical, fiscal, administrative, and quality improvement staff may be addressed and accommodated in the formulary system.

Therapeutic considerations

The two key therapeutic considerations for any new product are safety and efficacy. Ideally, these are documented by controlled, randomized, clinical trials in the peer-reviewed literature. In many cases, supporting data may be scarce or unpublished, in which case anecdotal data or abstracts assume greater importance. Specific considerations that enter into

these discussions are mechanism of action, adverse effects, contraindications, and drug interactions.

Limiting the number of drugs in the formulary, which has distinct economic advantages, is sometimes accomplished through the use of generic equivalents. If a generic product becomes available for a brand name product (as will eventually be the case with ReVia), the pharmacy must decide whether the new product is equivalent to the approved product. If so, it will recommend that the generic product be added to the formulary and will strongly encourage its use.

The use of therapeutic equivalents may also help control drug costs without sacrificing quality. If, for example, there were four drugs in a class, all of which were shown to be therapeutically equivalent, the P T committee might recommend that the institution place all four products on the formulary but stock only the least expensive product. The goal would be to stock and dispense the drug that does the greatest good for the greatest number of patients but to retain the capacity to serve the occasional patient for whom that product is for some reason unsatisfactory.

Cost impact

The first step in a fiscal analysis is to determine the drug's impact on the pharmacy budget. If the P T committee determines that the drug is safe and effective and that its effect on the pharmacy budget will be neutral or positive, it will generally recommend that the product be approved.

The costs of naltrexone include the costs of the medication itself (approximately $116 to the pharmacy for a bottle of 30 tablets) and the need for baseline and follow-up liver function tests ($30 total over the 3-month period). Thus, the costs associated with a 3-month treatment episode using 50 mg daily would be approximately $370 (although the price would be higher if naltrexone were purchased by a retail pharmacy). If patients do not routinely receive physical examinations or psychiatric examinations, these would represent additional costs. While these costs may not be a problem for private practitioners whose patients can be reimbursed by insurance, they may pose real fiscal challenges for public systems in which budgets are fixed. DuPont Pharma's exclusive right to market naltrexone for use in alcohol dependence expired in December 1997. If a generic version now becomes available, the costs of treatment can be expected to decrease.

Because naltrexone is a new class of drug and will not replace existing medications, it will raise pharmacy costs. Physicians who want to add naltrexone to the formulary of their health care organization may wish to consider the application of a systemwide fiscal analysis because it may offer a better way to evaluate the cost-effectiveness of the drug. For example, the use of naltrexone could potentially result in cost savings elsewhere in the health care system (e.g., hospital care, detoxification services, domestic violence reduction) if it helps a proportion of patients avoid relapse to heavy drinking. These potential cost savings may be greatest among high and chronic users of the physical health and mental health systems (e.g., patients with serious medical illnesses that are exacerbated by drinking, patients with dual disorders). Unfortunately, at this time, potential cost savings associated with naltrexone can only be hypothesized because formal cost-effectiveness studies have not been completed.

P T committee recommendation

The P T committee meets to discuss the monograph and the results of the therapeutic and fiscal analyses. The individual who has requested that the drug be added to the formulary is often invited to participate in this meeting. The P T committee may also invite other knowledgeable individuals to serve as consultants. If the committee recommends adding the drug to the formulary, further financial analyses may be requested. The motion is eventually forwarded to the appropriate committees of the medical staff and to the quality improvement staff for final action.

Development of guidelines for use

Once the drug has been approved for the formulary, the pharmacy staff meets with members of the appropriate medical or surgical department to develop guidelines for drug use.

Drug use review

Approximately 1 year after the drug has entered the formulary, the pharmacy performs a drug use review. Results of this review are important because they indicate the impact of the drug on the patient population of the particular health care system, rather than on the population at large. In some cases, results of the review may indicate the need for in-service educational efforts to ensure that physicians are prescribing the drug appropriately.

HMO and MCO Systems Formularies

The process by which new drugs are added to the formulary in HMO and MCO systems are generally based on--and similar to--those used in university-based systems. However, depending on the size of the health care organization, the process may be somewhat less structured.

The experience at Kaiser-Permanente may be typical of many large HMOs. Within this health care organization, the request is usually generated by a participating physician. Kaiser's P T committee is composed of staff members at various sites. In addition to evaluating individual clinician requests as they are received, the committee keeps an eye on new drugs in the FDA pipeline. It gathers information on these products in order to be prepared to review them once they are approved.

The drug review is done at a central level, as is drug purchasing. Kaiser's P T committee reviews information collected and analyzed by the pharmacy's drug information service and makes its recommendation on the basis of that data.

Decisionmakers at HMOs are favorably impressed by published data in the peer-reviewed literature. If such information is not available, anecdotal data can be persuasive. In some cases, the product is put on the formulary as an interim measure, and use of the product is monitored carefully. The final decision on adding the product to the formulary is based on local experience, as well as reports published since the original review took place.

Some MCOs have expressed fears of legal reprisal for not making drugs available to their patients. This is based on the belief that if there is no alternative drug, a new drug must be available to the patient, regardless of its cost or its risk-benefit ratio. Advocacy groups for patients with AIDS and other terminal illnesses often present powerful cases for action and insist that a new product be put on formularies for publicly funded as well as private health care organizations.

This situation poses ethical, as well as clinical and fiscal questions. Issues of this nature should be referred for discussion to the facility's legal and administrative staff. Of key importance in such deliberations is the need to define the current standard of care for a particular condition or disease and to determine whether the product is necessary to meet that standard. If a drug is added to a formulary primarily to reduce the potential of legal liability, the drug use review process may eventually have a key role in producing new evidence that will help demonstrate whether it is indeed safe and effective.

State Prescription Drug Formularies

Before a patient receiving publicly funded health care can receive naltrexone or any other prescription drug, that product must be on the State prescription drug formulary. Responsibility for maintaining and revising such a formulary is usually delegated to a unit or board within the State public health care system. In some States, the State Board of Pharmacy also has a role in drug approval.

Policies regarding selection of and reimbursement for drugs provided to patients on medical assistance vary. Health care providers who become involved in this process must familiarize themselves with the particular policies of their own State. The following two examples, drawn from the experience of two Consensus Panel members, illustrate the variety of ways in which States approach this issue.

Washington

In the State of Washington, a board of the State Medical Assistance Administration (MAA) has responsibility for making decisions about adding drugs to the State formulary. On learning that naltrexone had received FDA approval for use as an adjunct to alcohol treatment, MAA board members consulted with the State Division of Alcohol and Substance Abuse (DASA). MAA and DASA agreed to conduct a pilot project to determine whether naltrexone would be effective for individuals receiving publicly funded alcoholism treatment. DASA then approached two substance abuse treatment programs in Seattle to explore their interest in conducting the pilot project. Although these providers were familiar with the positive reports in the peer-reviewed literature, MAA board members wanted to ensure that the results would be applicable to the treatment of indigent persons receiving publicly funded treatment (see Appendix C for a description of the pilot project).

The results of the pilot project were quite positive, indicating that 42 percent of patients completed 90 days of outpatient substance abuse treatment while on naltrexone; 72 percent reported a decrease in alcohol craving, and the reported side effects were generally minimal and short-lasting (i.e., less than 2 weeks' duration). Both the treatment counselors and the physician who participated in the pilot project reported positive experiences and recommended that naltrexone be used as an adjunct to the treatment of alcohol dependence (Division of Alcohol and Substance Abuse, Department of Social and Health Services, State of Washington, 1995).

On the basis of these results, MAA added naltrexone to the Washington State Prescription Drug Program for the treatment of alcohol dependence. Shortly thereafter, the director of DASA sent a memorandum to certified substance abuse treatment providers statewide informing them of the results of the pilot project and of MAA's decision to add naltrexone to the formulary. A summary of the published literature concerning naltrexone, a description of the Seattle pilot project, indications for use, and various authorization forms necessary to prescribe naltrexone were included in the mailing (Division of Alcohol and Substance Abuse, Department of Social and Health Services, State of Washington, 1995).

California

To reduce administrative costs, California has delegated responsibility to the counties for decisions concerning the care of patients receiving publicly funded medical assistance. Using funds allocated by the State, each county is expected to either provide such care internally or contract with an HMO to provide the care.

In this situation, the decision to place naltrexone on the formulary is made at the county or HMO level. Members of each county's medical association provide input into HMO standards of care, including issues related to the use of prescription medications.

Getting Naltrexone on the Formulary: Strategies for Substance Abuse Treatment Providers

In addition to treatment providers becoming familiar with therapeutic and cost issues related to the use of naltrexone, the Consensus Panel recommends that they employ strategies such as the following:

- **Keep informed of State and local policies**. The health care environment is changing, and practices differ from State to State and from organization to organization. Substance abuse treatment providers must not only inform themselves of existing policies, but must also keep an eye on the horizon for possible changes and provide input when there are opportunities to do so.
- **Keep abreast of research**. In addition to keeping up with literature in peer-reviewed journals, substance abuse treatment providers should explore other sources. This can be done through networking and informed use of data available on the Internet. (See Figure B-2 for a listing of Federal and private Web sites that may be useful.) Staff of programs affiliated with an academic health center may wish to explore information available through the University Hospital Consortium, a membership organization. It sponsors a Technology Assessment Group that provides objective evaluations of new drugs and equipment.
- **Make strategic allies**. Treatment providers can forge alliances with three key groups: pharmacists, physicians, and fiscal analysts. Each brings special value to the drug-approval and drug-use processes:

Pharmacists are medication use experts. As part of the practice of pharmaceutical care, more and more pharmacists interact daily with physicians, other health professionals, and patients and their families in ambulatory, community, and inpatient settings. Substance abuse treatment providers in need of sound information can turn to pharmacists for advice about naltrexone. Other counselors and health care providers who are already well versed in the use of this drug may take a proactive role in sparking pharmacist interest in naltrexone. Pharmacists, in turn, can share their insights with prescribers.

- *Physician* support is essential.
- *Fiscal analysts* who have the ability to take a systemwide perspective on drug costs can be strategic partners in efforts to secure approval of naltrexone. Once informed of the clinical and financial implications of sobriety, they can help devise ways of documenting its cost-effectiveness on large scales.

Conclusion

Regardless of its importance, getting naltrexone on the formulary, one Panelist observed, is a "smaller piece of the problem." Ensuring that naltrexone is appropriately used in the treatment of alcohol dependence may be even more challenging. Achieving this goal requires educational efforts directed at policy makers, prescribers, pharmacists, health administrators, patients, and the public at large. Use of this TIP can facilitate that educational effort and improve patient access to naltrexone for the treatment of alcohol dependence.

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Appendix C --Translating Research Into Practice

Why Isn't Naltrexone More Widely Used?

Naltrexone has demonstrated efficacy as an important adjunct to the treatment of alcohol dependence, and it is available for general practitioners to prescribe. Yet it has not been widely accepted or tried. The media promoted naltrexone (ReVia) intensively when it was initially approved by the Food and Drug Administration for use in the treatment of alcoholism, and the pharmaceutical company that manufactures and distributes naltrexone used standard, but limited, marketing techniques to publicize the drug. Yet the field has been slow to adopt the use of naltrexone.

There may be several reasons for this. First, because the initial studies were relatively small and ongoing research was pending, some practitioners have adopted a wait-and-see approach. The additional costs associated with naltrexone may also serve to limit its use. Finally, the fact that there is typically a long lag between an invention or a new research finding and its adoption and widespread use by individual practitioners or programs and organizations in the field has been extensively documented (National Institute of Mental Health [NIMH], 1971; Backer, 1991). Even though the Federal Government spends millions of dollars annually to support carefully selected research and service demonstrations as well as medications development, many practical, effective, and innovative new technologies and procedures languish in published articles in scientific journals without further application. The reasons for this apparent gap between research and its application have also been extensively studied with increasing intensity following the implementation of Great Society programs and the War on Poverty during the 1960s and 1970s. In fact, knowledge development and application has become a professional field with its own scholarly journals, bibliographies, and government-supported or nonprofit research institutes and university-based programs. These activities are known under various rubrics as technology transfer, information dissemination, research utilization, diffusion of innovation, policy research, and organizational change efforts (Backer, 1991). Some of the general tenets of this field that seem applicable to the planned use of naltrexone as a new tool for the treatment of alcohol dependence are summarized in the paragraphs that follow.

Investigators have identified a number of reasons why research findings and innovative technologies are not readily adopted in the field. Among the most commonly cited causes are the inadequate strategies used for disseminating new knowledge and the different perspectives of researchers and practitioners.

Not only does publication of research findings take an excessive amount of time, but the journals in which articles appear are seldom read by more than a few interested professionals and not regularly by those practitioners most likely to benefit from the results (NIMH, 1971). Moreover, research findings are not usually packaged in readily understandable language with clearly specified recommendations that practitioners can replicate in their own programs. Scholarly articles often contain extensive details that are of little interest to busy practitioners (Backer, 1991).

Other frequently cited reasons for the failure to apply research findings or adopt innovations include the threats that change poses to an organization and its staff, the lack of readily available resources needed to implement the change, and the uncertainty about whether the innovation will actually work as well in another setting or with a different target population than the one used for the original research (NIMH, 1971; Backer, 1991). Figure C-1 lists four critical challenges to the effective use of research findings identified by one investigator in this area.

Strategies That Encourage Technology Transfer and Research Utilization

Researchers have noted that certain characteristics of both the innovation and the organizations and professionals that are considering its adoption affect the probability that a new, but tested, methodology or procedure will be successfully incorporated into routine practice (NIMH, 1971). Some of these characteristics are summarized in Figure C-2.

Strategies Specific to Naltrexone Pharmacotherapy

Although patients and family members may be stimulated by media publicity about naltrexone to ask questions of their treatment providers or physicians, they do not have the necessary influence and authority to actually get a prescription if their inquiries are met with indifference or overt rejection. Because incorporation of naltrexone into the alcohol dependence treatment spectrum is not an automatic response--even though the medication's safety and efficacy have been demonstrated--programs that want to adopt its use may need a planned strategy. The following steps should be considered in applying the research findings on the use of naltrexone. The steps may be conducted in any order or simultaneously:

- *Disseminate information about naltrexone* to all levels of the health care organization, including treatment providers, ancillary staff, and patients who need to become aware of the drug, its demonstrated efficacy in the treatment of alcohol dependence, and its safety. Start by conveying basic information. Information can be presented in printed materials but is more likely to be assimilated if delivered through in-service training, media presentations, or conferences. Make certain that information is translated into language the audience understands and that the content is targeted to the audience's needs.
- *Identify advocates and build alliances among them* to ensure a climate of acceptance and support for use of the medication. Advocates can also be used as potential consultants or facilitators of the change process. Potential resources include the following:
  - State substance abuse authority
  - American Council on Alcoholism
  - State psychological associations
  - National Alliance for the Mentally Ill (NAMI)
  - Washington Alliance for the Mentally Ill (WAMI)
  - Researchers who have investigated naltrexone
  - State medical society members
  - American Society of Addiction Medicine (ASAM) members
  - National Association of Alcohol and Drug Abuse Counselors
  - Staff and directors of existing treatment programs that show success in using naltrexone
  - Representatives from Employee Assistance Programs (EAPs), criminal justice system offices of probation and parole, or other health care providers who have witnessed positive responses to naltrexone as an adjunct to the treatment of alcohol dependence
  - Consumers and family members who can move prescribers to try the drug
- *Enlist the support of influential administrators and organizational leaders* whose endorsement will be necessary for incorporating naltrexone into the treatment protocol. The probability that this medication will be used appropriately is increased dramatically if leaders express enthusiasm for its adoption or actively assist with its introduction (e.g., by issuing directives, by making funding and other necessary resources available).
- *Determine which perceived needs and problems of the organization and consumers could be alleviated by the introduction of naltrexone.* Motivation to introduce change is enhanced by heightened sensitivity to specific problems such as high rates of relapse or early treatment termination among alcohol-dependent patients in the treatment program or among specific subsets of this population (e.g., patients with dual disorders). Pressure for change can come from patients and families who experience repeated treatment failures with the current protocols or from staff members who are dissatisfied with patients' progress.
- *Arrange personal contacts between staff members of the organization that is considering naltrexone and persons who have first-hand knowledge of its safety and utility*, which might include the form of consultation provided by outside experts.
- *Acquire direct experience with naltrexone* by setting up a small pilot demonstration or an open-label trial for approximately 20 to 50 appropriately selected patients to see how

they respond compared with baseline functioning after 3 to 6 months on naltrexone as an adjunct to standard treatment. This is ultimately the most convincing evidence that the medication is appropriate for the population of patients served by the provider or program. It is also a useful way to discover resistance to the use of naltrexone or other unanticipated administrative problems. If naltrexone is not already on the formulary or covered by patients' insurance, the pharmaceutical company that distributes naltrexone is often willing to make the drug available for a limited period of time for indigent patients who cannot afford to pay for it. Because many physicians are only comfortable prescribing drugs with which they have become familiar and are reluctant to try new ones without backup, a pilot demonstration that includes an experienced medical consultant and necessary laboratory resources may be a useful mechanism for introducing the drug into practice.

- *Recognize and overcome resistance that can undermine innovation.* In the case of naltrexone, resistance is likely to come from several sources: (1) opposition to any type of pharmacotherapeutic support as part of "drug-free" treatment, (2) the incremental costs added to an already overburdened treatment system by the expenses incurred in prescribing naltrexone and providing for laboratory monitoring of liver functioning, (3) difficulties in coordinating medical services with appropriate psychosocial supports in systems that have not relied heavily on physician involvement, (4) threats to the job security of nonmedically trained counselors, and (5) lack of a basic understanding of the brain mechanisms of addiction.

Some staff members and patients in alcohol treatment programs with an Alcoholics Anonymous (AA)-type orientation and philosophy may resist the introduction of any type of pharmacotherapy because they view this as a "crutch" substituted for personal responsibility and the support of peers in self-help groups. Staff members may also believe that immediate discharge is necessary if abstinence is not maintained from the point of treatment entry. However, naltrexone may help prevent relapse among those who slip. Some AA and Narcotics Anonymous (NA) groups and outpatient "drug-free" treatment programs have come to accept concurrent pharmacotherapy for depression or other mental disorders and even methadone-maintained patients. Educating staff and patients in these treatment systems about the biochemical changes in the brain that alcohol and other drug dependence cause may be useful. It should be emphasized that such changes are treatable and often reversible with pharmacotherapeutic agents that help reestablish normality of brain functions and behaviors so that rehabilitation can take place through counseling and other therapeutic services (National Institute on Drug Abuse, 1996). Naltrexone may be more readily accepted by mental health systems and their patients or opioid treatment programs that already rely on pharmacotherapy as an appropriate treatment adjunct.

Another point of resistance may be the incremental costs added per patient to the treatment of alcohol dependence. In such situations, the arguments of experts will need to be carefully tailored to the realities that programs face. Unfortunately, studies on the cost-effectiveness of naltrexone have not yet been completed. As a result, potential cost offsets can only be suggested.

Some persuasive points may be that naltrexone is becoming an appropriate standard of care for refractory alcohol-dependent patients and that naltrexone is not very costly compared with other drugs prescribed for chronic medical illnesses. The use of naltrexone may lead to cost savings elsewhere in the health care system (e.g., hospital care, detoxification services, domestic violence reduction). For example, if serious relapse is prevented, then there may be reductions in the use of hospital care detoxification services or prevention/reduction of medical illnesses. The largest cost savings may be among high and chronic users of the physical health and mental health systems (e.g., patients with serious medical illnesses that are exacerbated by drinking, patients with dual disorders), although no data have yet been compiled to confirm this effect.

Ethnicity and culture may play important roles in the acceptability of naltrexone by patients as well as by health care system representatives. Language issues are always important, as are different cultural attitudes toward the use of medications and psychosocial therapies. Cultural sensitivity is essential in establishing an appropriate treatment program environment.

Problems may also be posed and resistance encountered because naltrexone requires coordination of medical and psychosocial approaches that are not always well integrated in current substance abuse treatment modalities. These difficulties are best addressed by careful, but flexible, planning. The case studies that are presented in this appendix offer examples of how naltrexone can be effectively incorporated into a community mental health center program and into a State-certified substance abuse treatment program.

Preparing the System for Using Naltrexone as a Treatment Adjunct

A carefully developed plan for adopting an innovation to a new setting is essential for its success. All staff members who will be involved in using naltrexone should be included in planning for its introduction so that their needs are considered and they develop some "ownership" of the process, thereby decreasing resistance to the change (Backer, 1991). The following steps should be completed before naltrexone is introduced:

1. *Identify the prescriber before introducing naltrexone.* The system or program should make certain this person is fully educated about the appropriate use of this pharmacotherapy and is convinced that naltrexone can be an effective adjunct to the treatment of alcohol dependence for well-selected patients.

2. *Educate all members of the system/program about naltrexone* at the level of knowledge necessary for their assigned roles. Some resources are available from the pharmaceutical company for this purpose. DuPont Merck has publications directed to physicians, counselors, and patients.

3. *Educate and/or train* treatment program admissions coordinators about naltrexone and have coordinators identify naltrexone candidates at the time of intake.

4. *Make certain that naltrexone is available* on the Medicaid formulary or through insurance reimbursement and special programs for indigent patients (see Appendix B).

5. *Ensure coordination with appropriate psychosocial components* that are already available as standard care or that are specially developed or enhanced. As part of a comprehensive treatment program, refer to 12-Step programs such as AA, NA, or other groups that are known to accept patients who are using prescribed drugs.

6. *Develop and disseminate a formal protocol* that includes criteria and procedures for screening and admitting patients; conducting the initial and followup physical evaluations; referring patients for additional medical services and psychosocial therapy; discharging, extending, and terminating patients from naltrexone treatment and the addictions program; handling any emergencies that may occur; and evaluating the effectiveness of the program.

Case Study 1: Starting a Naltrexone Treatment Program in a Community Mental Health Center

An urban community mental health center (CMHC) in Illinois successfully integrated naltrexone treatment into available services for indigent patients with dual disorders. The CMHC instituted a flexible approach to coordinated care and enlisted the vital support of its medical director. Although an addictions treatment program was associated with the CMHC, its staffing, administration, and protocols were different and separate from the psychological and psychiatric services. Moreover, it was the policy of the addictions treatment component to discharge any patient immediately who relapsed into drinking (or drug using) and to terminate all contact with the CMHC, even if the patient was receiving pharmacotherapy for a mental disorder. This problem was addressed by simultaneously enrolling patients with dual disorders into both the addictions treatment and the medical services components so they could continue to have physician appointments after compulsory discharge from the addictions treatment program.

Because the CMHC administered different services (such as psychotherapy, group therapy, case management) under different programs, coordination of care was administratively complex. A nurse from the CMHC's medical services program was assigned responsibility for coordinating care for all patients who were taking naltrexone regardless of program. In addition to physician visits for prescription of naltrexone, patients continued their participation in whatever psychosocial treatments were appropriate for their particular psychiatric illness. Patients were not required to participate in traditional addictions treatment, primarily because most of the patients were unwilling or inappropriate for such programs. In practice, this individualized psychosocial treatment was more effective than previously fixed programmatic requirements, especially for patients who were unable to achieve abstinence immediately. Patients could also receive naltrexone at no cost through the pharmaceutical company's special program for indigent patients.

The coordinated and individualized approach exposed many staff members in a variety of service components to patients who were taking and responding to naltrexone. The improvements in patients taking naltrexone quickly stimulated the interest of these treatment providers and generated patient referrals. These patients were being followed in psychological support programs but had either refused or failed treatment in the addictions program. Individualized psychosocial care for patients with dual disorders who were taking naltrexone was particularly effective.

The clinical records of 72 patients with dual disorders who were treated with naltrexone were reviewed. Diagnoses included

- Major depression (*n* = 37)
- Schizophrenia (*n* = 17)
- Bipolar illness (*n* = 11)
- Schizoaffective disorder (*n* = 7)
- Transsexualism (*n* = 4)

Concurrent psychotropic medications included antidepressants, neuroleptics, lithium, divalproex, benzodiazepines, disulfiram, atypical antipsychotics, and estrogens.

Although common adverse effects (mostly nausea) during the first 2 weeks were noted in 26 percent of the patients who began taking naltrexone, only 11 percent found the effects severe enough to discontinue the medication. The response to naltrexone among these patients with coexisting disorders was impressive, with 59 patients (82 percent) achieving at least a 75-percent reduction in alcohol intake and only 2 patients (2.8 percent) having less than a 25-percent reduction in their alcohol consumption.

This CMHC concluded that the following factors were most helpful in the successful introduction of naltrexone treatment into the organization:

- Administrative support at the top level, in this case by the CMHC's medical director

- Coordination by a single person or service given the time and authority to schedule patients across services for needed psychosocial and medical care

- Flexibility in arranging services so that psychosocial components were individualized for the different and changing needs of the patients

- Allowing patients treated with naltrexone to continue in various psychosocial interventions with assorted agency staff so that patients' actual positive responses to naltrexone and their success in avoiding relapse were more persuasive and convincing than words or in-service training. In fact, formal education about naltrexone was most effective after staff members had already been convinced of the drug's efficacy by contact with successful patients.

Case Study 2: Use of Naltrexone as a Treatment Supplement for Patients In Publicly Funded Treatment Programs

The Washington State agency for alcohol and substance abuse used a small and informal pilot project to demonstrate the effectiveness of naltrexone as a supplemental adjunct in the standard treatment of alcohol dependence. The results of the pilot project, together with the already available research literature, were sufficiently convincing for the State Medical Assistance Administration to add naltrexone to the State's formulary for qualified patients in publicly supported alcohol- and opioid-dependence treatment programs. These patients must be enrolled in State-certified substance abuse treatment programs that have been authorized to use naltrexone. The patients must get the prescription from a physician and must have a current medical identification card that is not restricted to emergency care, family planning services, or other specified limitations.

A protocol and forms were designed so that counselors in the substance abuse treatment programs could recommend naltrexone, obtain consent from patients to add the medication to the treatment plan, and issue naltrexone authorization cards that would allow patients to receive (and pharmacies to be reimbursed for) naltrexone capsules for a 3-month period (12 weeks). The protocol included three prescriptions of a 34-day supply, provided that no more than two unauthorized breaks in treatment would occur. The authorization cards required patient consent for disclosure of confidential information for 90 days to the patient's private physician and a designated pharmacy.

Counselors were also instructed to confer with and regularly record the reactions and treatment progress of patients who agreed to use naltrexone. It was also recommended that issues pertaining to naltrexone use be discussed in individual counseling sessions rather than in groups where any reports of early common adverse effects might deter other patients from considering the use of naltrexone. Counselors were encouraged to incorporate naltrexone into the treatment regimen; to inform themselves about its efficacy; to educate patients about the medication, using materials available from the pharmaceutical company that supplies naltrexone; and most important, to "pass this information on to all physicians [they] may have contact with."

During 1995, the pilot project enrolled a total of 50 patients with alcohol dependence from two outpatient substance abuse treatment programs in Seattle, Washington, with the following results:

- 42 percent ($n = 21$) completed 90 days of treatment while taking naltrexone.

- 10 percent ($n = 5$) relapsed to drinking and stopped taking naltrexone.

- 15 percent ($n = 7$) stopped taking naltrexone due to reported common adverse effects, including nausea; feeling wired, jittery, or restless; hot flashes; weight loss or a decrease in appetite; or headache. Most common adverse effects dissipated after 2 weeks, and physicians at the participating facilities split doses or decreased them to reduce patient-reported symptoms.

- 15 percent ($n = 7$) quit taking naltrexone because they felt they did not need it and believed they could stay sober on their own, using learned skills and other supports.

- 50 percent ($n = 25$) reported no alcohol consumption while taking naltrexone.

- 72 percent ($n = 36$) reported a decrease in the craving for alcohol while taking naltrexone.

- 72 percent of the patients who did resume drinking ($n = 18$ of 25) while taking naltrexone consumed less alcohol than they usually did before starting the medication.

- Women appeared to respond more readily to naltrexone than did men, and the women showed better outcomes from use of naltrexone.

- Patients experienced some difficulty in making an initial connection with the prescribing physician.

- Patients required close monitoring for the first 2 weeks that they took naltrexone. The recommended practice during this time was to discuss medication issues in individual counseling sessions, not in group therapy.

- Naltrexone also appeared to have a positive effect on concurrent use of other drugs in addition to alcohol, as evidenced by a decrease in the number of positive urinalysis results for other drugs.

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Appendix D --Instruments

This appendix includes

- Alcohol Urge Questionnaire
- Obsessive Compulsive Drinking Scale

Alcohol Urge Questionnaire

Listed below are questions that ask about your feelings about drinking. The words "drinking" and "have a drink" refer to having a drink containing alcohol, such as beer, wine, or liquor. Please indicate how much you agree or disagree with each of the following statements by placing a single mark (like this: X) along each line between STRONGLY DISAGREE and STRONGLY AGREE. The closer you place your mark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling *right now* as you are filling out the questionnaire.

RIGHT NOW

1. All I want to do now is have a drink.

   STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

2. I do not need to have a drink now.

   STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

3. It would be difficult to turn down a drink this minute.

   STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

4. Having a drink now would make things seem just perfect.

   STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

5. I want a drink so bad I can almost taste it.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

6. Nothing would be better than having a drink right now.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

7. If I had the chance to have a drink, I don't think I would drink it.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

8. I crave a drink right now.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

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Obsessive Compulsive Drinking Scale

Directions: The questions below ask you about your drinking alcohol and your attempts to control your drinking. Please circle the number next to the statement that best applies to you.

1. How much of your time when you're not drinking is occupied by ideas, thoughts, impulses, or images related to drinking?

    0.)None
    1.)Less than 1 hour a day
    2.)1-3 hours a day
    3.)4-8 hours a day
    4.)Greater than 8 hours a day

2. How frequently do these thoughts occur?

    0.)Never
    1.) No more than 8 times a day
    2.)More than 8 times a day, but most hours of the day are free of those thoughts
    3.)More than 8 times a day and during most hours of the day
    4.)Thoughts are too numerous to count, and an hour rarely passes without several such thoughts occurring.

*Insert the Higher Score of Questions 1 or 2 here*_____

3. How much do these ideas, thoughts, impulses, or images related to drinking interfere with your social or work (or role) functioning? Is there anything you don't or can't do because of them? [If you are not currently working, how much of your performance would be affected if you were working?]

    0.)Thoughts of drinking never interfere--I can function normally.
    1.)Thoughts of drinking slightly interfere with my social or occupational activities, but my overall performance is not impaired.
    2.)Thoughts of drinking definitely interfere with my social or occupational performance, but I can still manage.
    3.)Thoughts of drinking cause substantial impairment in my social or occupational performance.
    4.)Thoughts of drinking interfere completely with my social or work performance.

4. How much distress or disturbance do these ideas, thoughts, impulses, or images related to drinking cause you when you're not drinking?

    0.)None
    1.)Mild, infrequent, and not too disturbing

    2.)Moderate, frequent, and disturbing, but still manageable

    3.)Severe, very frequent, and very disturbing

    4.)Extreme, nearly constant, and disabling distress

5. How much of an effort do you make to resist these thoughts or try to disregard or turn your attention away from these thoughts as they enter your mind when you're not drinking? (Rate your *efforts made to resist these thoughts*, not your success or failure in actually controlling them.)

    0.)My thoughts are so minimal, I don't need to actively resist. If I have thoughts, I make an effort to *always* resist.

    1.)I try to resist most of the time.

    2.)I make some effort to resist.

    3.)I give in to all such thoughts without attempting to control them, but I do so with some reluctance.

    4.)I completely and willingly give in to all such thoughts.

6. How successful are you in stopping or diverting these thoughts when you're not drinking?

    0.)I am completely successful in stopping or diverting such thoughts.

    1.)I am usually able to stop or divert such thoughts with some effort and concentration.

    2.)I am sometimes able to stop or divert such thoughts.

    3.)I am rarely successful in stopping such thoughts and can only divert such thoughts with difficulty.

    4.)I am rarely able to divert such thoughts even momentarily.

7. How many drinks do you drink each day?

    0.)None

    1.)Less than 1 drink per day

    2.)1-2 drinks per day

    3.)3-7 drinks per day

    4.)8 or more drinks per day

8. How many days each week do you drink?

    0.)None

    1.)No more than 1 day per week

    2.)2-3 days per week

    3.)4-5 days per week

    4.)6-7 days per week

Insert the Higher Score of Questions 7 or 8 here____

9. How much does your drinking interfere with your work functioning? Is there anything that you don't or can't do because of your drinking? [If you are not currently working, how much of your performance would be affected if you were working?]

    0.)Drinking never interferes--I can function normally.

    1.)Drinking slightly interferes with my occupational activities, but my overall performance is not impaired.

    2.)Drinking definitely interferes with my occupational performance, but I can still manage.

    3.)Drinking causes substantial impairment in my occupational performance.

    4.)Drinking problems interfere completely with my work performance.

10. How much does your drinking interfere with your social functioning? Is there anything that you don't or can't do because of your drinking?

    0.) Drinking never interferes--I can function normally.

    1.)Drinking slightly interferes with my social activities, but my overall performance is not impaired.

    2.)Drinking definitely interferes with my social performance, but I can still manage.

    3.)Drinking causes substantial impairment in my social performance.

    4.)Drinking problems interfere completely with my social performance.

Insert the Higher Score of Questions 9 or 10 here_____

11. If you were prevented from drinking alcohol when you desired a drink, how anxious or upset would you become?

    0.)I would not experience any anxiety or irritation.

    1.)I would become only slightly anxious or irritated.

    2.)The anxiety or irritation would mount, but remain manageable.

    3.)I would experience a prominent and very disturbing increase in anxiety or irritation.

    4.)I would experience incapacitating anxiety or irritation.

12. How much of an effort do you make to resist consumption of alcoholic beverages? (Only *rate your effort to resist*, not your success or failure in actually controlling the drinking.)

    0.)My drinking is so minimal, I don't need to actively resist. If I drink, I make an effort to always resist.

    1.)I try to resist most of the time.

    2.)I make some effort to resist.

    3.)I give in to almost all drinking without attempting to control it, but I do so with some reluctance.

    4.)I completely and willingly give in to all drinking.

13. How strong is the drive to consume alcoholic beverages?

    0.)No drive

    1.)Some pressure to drink

    2.)Strong pressure to drink

    3.)Very strong drive to drink

    4.)The drive to drink is completely involuntary and overpowering.

14. How much control do you have over the drinking?

    0.)I have complete control.

    1.)I am usually able to exercise voluntary control over it.

    2.)I can control it only with difficulty.

    3.)I must drink and can only delay drinking with difficulty.

    4.)I am rarely able to delay drinking even momentarily.

Insert the Higher Score of Questions 13 or 14 here_____

Appendix E --Resource Panel

Lonn Aussicker

    Public Health Analyst

    HIV Linkage Branch

    Division of Clinical Programs

    Center for Substance Abuse Treatment

    Rockville, Maryland

Johanna Clevenger, M.D.

    Chief

    Alcoholism and Substance Abuse Program Branch

    Indian Health Service

    Rockville, Maryland

Jerry Cott, Ph.D.

    Head

    Pharmacologic Treatment Program

    National Institute of Mental Health

    Rockville, Maryland

Dorynne Czechowicz, M.D.

    Associate Director

    Medical/Professional Affairs

    Treatment Research Branch

    Division of Clinical and Services Research

    National Institute on Drug Abuse

    Rockville, Maryland

Gil Hill

    Director

    Office of Substance Abuse

    American Psychological Association

    Washington, D.C.

Lt. Col. Kenneth J. Hoffman, M.D., M.P.H., M.C.F.S.

    Director, Center for Addiction Medicine

    Center for Training and Education in Addiction Medicine (C-Team)

    Department of Preventive Medicine/Biometrics

    Uniformed Services University of the Health Sciences

    Bethesda, Maryland

Jeffrey T. Kramer

Executive Vice President

National Treatment Consortium

Washington, D.C.

Raye Z. Litten, Ph.D.

Program Officer

Treatment Research Branch

Division of Clinical and Prevention Research

National Institute on Alcohol Abuse and Alcoholism

Kensington, Maryland

Patrice Muchowski, Sc.D.

Vice President

Clinical Services

Adcare Hospital of Worcester

Worcester, Massachusetts

Eleanor Sargent

Director

Clinical Issues

The National Association of Alcoholism and Drug Abuse Counselors

Arlington, Virginia

Terry K. Schultz, M.D.

Colonel/Chief

Alcohol and Drug Addiction Services

Consultant to the Army Surgeon General

United States Army Medical Corps

Falls Church, Virginia

Appendix F --Field Reviewers

Dorynne Czechowicz, M.D.

Associate Director

Medical/Professional Affairs

Treatment Research Branch

Division of Clinical and Services Research

National Institute on Drug Abuse

Rockville, Maryland

Deborah Duran, Ph.D.

Research and Policy

National Coalition of Hispanic Health

Washington, D.C.

John E. Emmel, M.D.

Medical Director

Department of Alcohol and Other Drug Abuse Services

Mount Pleasant, South Carolina

Arthur C. Evans, Ph.D.

Director

Managed Care

Connecticut Department of Mental Health and Adolescent Services

Hartford, Connecticut

Michael Fingerhood, M.D.

Associate Professor of Medicine

Department of Chemical Dependence

School of Medicine

Johns Hopkins University

Baltimore, Maryland

Mark S. Gold, Ph.D.

Professor

Department of Neurosciences, Psychiatry, Community Health, and Family Medicine

University of Florida Brain Institute

Gainesville, Florida

Gil Hill

Director

Office of Substance Abuse

American Psychological Association

Washington, D.C.

Robert Holden, M.A.

Program Director

Partners in Drug Abuse Rehabilitation Counseling

Washington, D.C.

George Kanuck

Office of Policy Coordination and Planning

Center for Substance Abuse Treatment

Rockville, Maryland

Raye Z. Litten, Ph.D.

Program Officer

Treatment Research Branch

Division of Clinical and Prevention Research

National Institute on Alcohol Abuse and Alcoholism

Kensington, Maryland

Charles P. O'Brien, M.D., Ph.D.

Professor and Director

Treatment Research Center

University of Pennsylvania

Philadelphia, Pennsylvania

Patricia Reihl

Coordinator

Spring House

Paramus, New Jersey

Terry K. Schultz, M.D.

Colonel/Chief

Alcohol and Drug Addiction Services

Consultant to the Army Surgeon General

United States Army Medical Corps

Falls Church, Virginia

Richard B. Seymour

Director

Information and Education

Haight Ashbury Free Clinics, Inc.

San Francisco, California

David E. Smith, M.D.

Medical Director

Haight Ashbury Free Clinics, Inc.

San Francisco, California

Christopher J. Stock, Pharm.D.

Clinical Pharmacist

Substance Abuse Program

Veterans Medical Center

Salt Lake City, Utah

Richard T. Suchinsky, M.D.

Associate Chief

Addictive Disorders

Department of Veterans Affairs

Mental Health and Behavioral Sciences Services

Washington, D.C.

Roy L. Sykes, M.A.C., C.D.S. III

Services Supervisor

Therapeutic Health Services

Seattle, Washington

Joseph Volpicelli, M.D., Ph.D.

Associate Professor

Treatment Research Center

University of Pennsylvania

Philadelphia, Pennsylvania

[Figures]

Figure 2-1: Information on Naltrexone for the Primary Health Care Provider

Figure 2-1 Information on Naltrexone for the Primary Health Care Provider
■ Naltrexone is an appropriate treatment for alcohol-dependent patients, including binge drinkers.
■ The only absolute medical contraindications are liver failure, acute infectious hepatitis, and current dependence on opioids or active opioid withdrawal. Elevated bilirubin levels, pregnancy, breast feeding, and use in adolescents are relative contraindications.
■ At the currently recommended dose of 50 mg daily, hepatic toxicity is very unlikely. Continued alcohol use is more likely than naltrexone to cause liver damage.
■ Providers should perform LFTs prior to treatment initiation and periodically during treatment.
■ Abstinence should be a desired goal for the patient; however, reductions in drinking may be an acceptable intermediate outcome. Failure to maintain complete abstinence is not necessarily a failure of treatment because there are many other areas of a patient's life that can improve, such as job performance, social relationships, and general physical health. This is similar to the goal of reducing high blood pressure; not all patients will have a total improvement of hypertension.
■ Naltrexone is likely to be most effective when used in combination with other forms of treatment for alcoholism, such as psychosocial interventions, and when the patient complies with both.

Figure 2-2: Absolute and Relative Contraindications for Naltrexone

Figure 2-2 Absolute and Relative Contraindications for Naltrexone	
Absolute	**Relative**

■ Acute hepatitis	■ Significant hepatic dysfunction
■ Liver failure	■ Anticipated need for opioids to treat an identified medical problem[b]
■ Chronic opioid dependence or current opioid use, especially methadone or LAAM[a]	■ Pregnancy[c]
■ Active opioid withdrawal (Note: The naltrexone-clonidine combination can be used in opioid withdrawal procedures.)	■ Breast feeding[c]
	■ Use in adolescents[c]

[a]This includes not only illegal opiates such as morphine or heroin, but also opioid-containing medications that are prescribed for managing pain and treating serious medical conditions such as heart disease, severe arthritis, sickle cell anemia, and recurrent congestive heart failure.

[b]For individuals who are taking naltrexone, prescription or over-the-counter analgesics, cough medicines, and pain medications that contain opioids--such as oxycodone hydrochloride (e.g., Percodan), hydrocodone bitartrate (e.g., Vicodin), and codeine (e.g., Robitussin A-C)--may not be effective. Naltrexone does not affect nonsteroidal anti-inflammatory drugs (e.g., Advil, Aleve), aspirin, or acetaminophen (e.g., Tylenol). Naltrexone blocks the effect of loperamide hydrochloride (Imodium) against diarrhea. Bismuth compounds (Pepto-Bismol) may be used for mild nausea or diarrhea, and octreotide acetate (Sandostatin) may be used for severe diarrhea, and ondansetron hydrochloride (Zofran) may be used for nausea and vomiting, especially with accidental naltrexone-precipitated opiate withdrawal.

[c]Until further research is done, due to the effects of naltrexone on hormonal status, especially growth hormone, luteinizing hormone, and prolactin.

Figure 2-3: Elements of Pretreatment Workup

Figure 2-3 Elements of Pretreatment Workup
■ Physical examination of the liver and thorough laboratory screening of liver function
■ Laboratory tests including 　■ Serum aminotransferases 　■ Total bilirubin 　■ Pregnancy test (urine or blood) 　■ Urine toxicology screen
■ Complete/updated medical history
■ Substance use/abuse history combined with a screening for signs and symptoms of recent narcotic use
■ Mental health/psychiatric status screening with a focus on anxiety, depression, psychosis, and level of cognitive functioning

Figure 2-4: Dosing Strategies for Starting Naltrexone Treatment [a]

Figure 2-4 Dosing Strategies for Starting Naltrexone Treatment[a]	
General Approach	**Specialized Approach**

■ For most patients ■ 50 mg/day	■ For patients judged likely to be at risk for adverse effects, such as younger patients and those with shorter durations of abstinence. ■ 12.5 mg/day or 25 mg/day for a few days, then gradually increase to 50 mg daily. This dose can be divided into two doses, each with a meal if desired.

Note: If severe common adverse effects occur after the initial dose, stop the medicine, then resume at a lower dose 1 or 2 days after the symptoms have subsided.

[a] Treatment with naltrexone should be tailored to patient needs. Dosing strategies described are examples of models used by some programs; they do not represent definitive guidelines.

Figure 2-5: Safety Identification Card

Figure 2-5
Safety Identification Card

Side 1

TO MEDICAL PERSONNEL TREATING ME IN AN EMERGENCY:

This patient is taking the oral opioid antagonist reVia , formerly known as Trexan (naltrexone hydrochloride).

In an emergency situation in patients receiving fully blocking doses of reVia ,a suggested plan of management is regional anesthesia, conscious sedation with a benzodiapine, use of non-opioid analgesics, or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic that minimizes the curation of respiratory depression is preferred. The amount of analgesia administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythemia, or bronchoconstriction), presumably due to histamine release.

Irrespective of the drug chosen to reverse reVia (naltrexone hydrochloride) blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

For medical emergencies, call your regional Poison Control Center.
Further information may be obtained by calling: 1-800-4PHARMA.

Side 2

The name and telephone number of physician who prescribed reVia (naltrexone hydrochloride).

Physician's name: _____

Physician's telephone: _____

Patient's name: _____

Patient's telephone: _____

Date treatment was initiated: _____

Figure 3-1: The Structure of Typical Neurons in the Brain
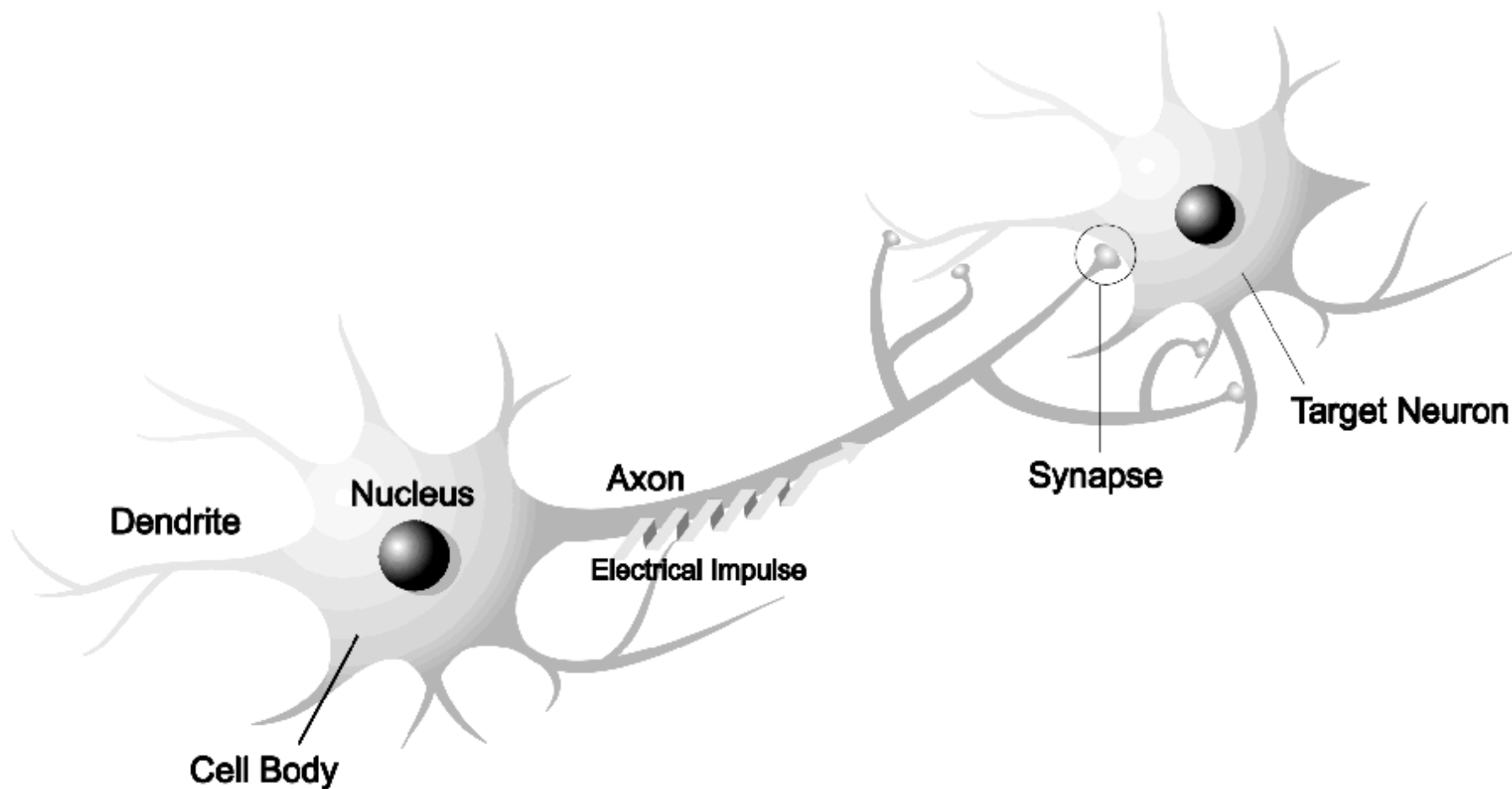
Figure 3-1
The Structure of Typical Neurons in the Brain

Figure 3-2: How Neurons Communicate

Figure 3-2
How Neurons Communicate
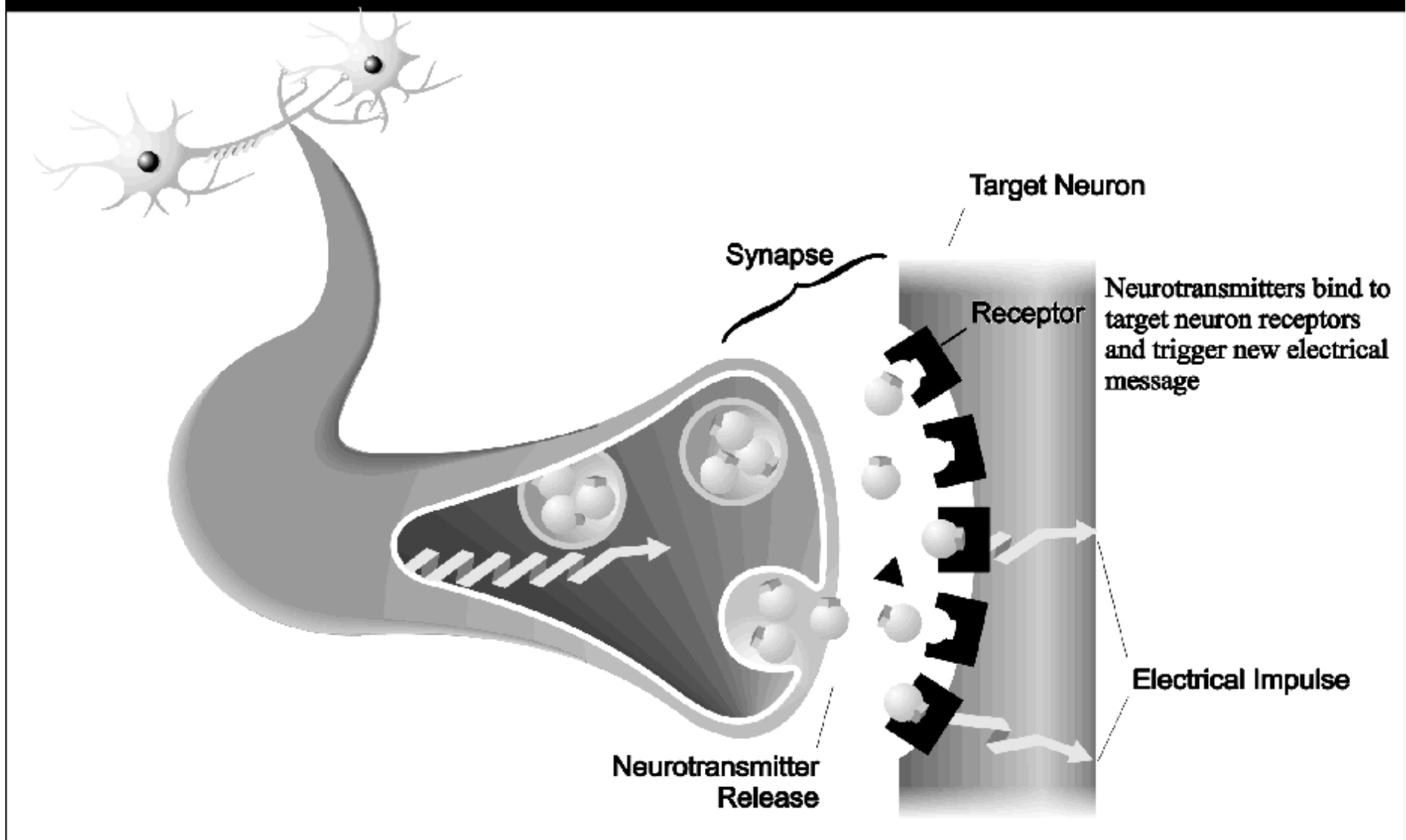
Figure 3-3: Opiates Versus Opioids

Figure 3-3
Opiates Versus Opioids

■ Opiates such as morphine and heroin are derived from opium, which is harvested from the opium poppy (*Papaver somiferum*). Through their research on opiate addiction, scientists discovered specific sites in the central nervous system where opiates attach and exert their effect. These sites are called opioid receptors. Subsequent to this discovery, scientists were able to identify the naturally occurring chemicals produced by the body that also attach to opioid receptors.

■ In this document, the term *opiate* refers to drugs like morphine and heroin, whereas the term *opioid* refers to naturally occurring chemicals such as enkephalins and endorphins (endogenous opioids) that exert opiate-like effects by interacting with central nervous system opioid receptors.

Figure 3-4: The Viscious Circle of Addiction

Figure 3-4
The Vicious Circle of Addiction
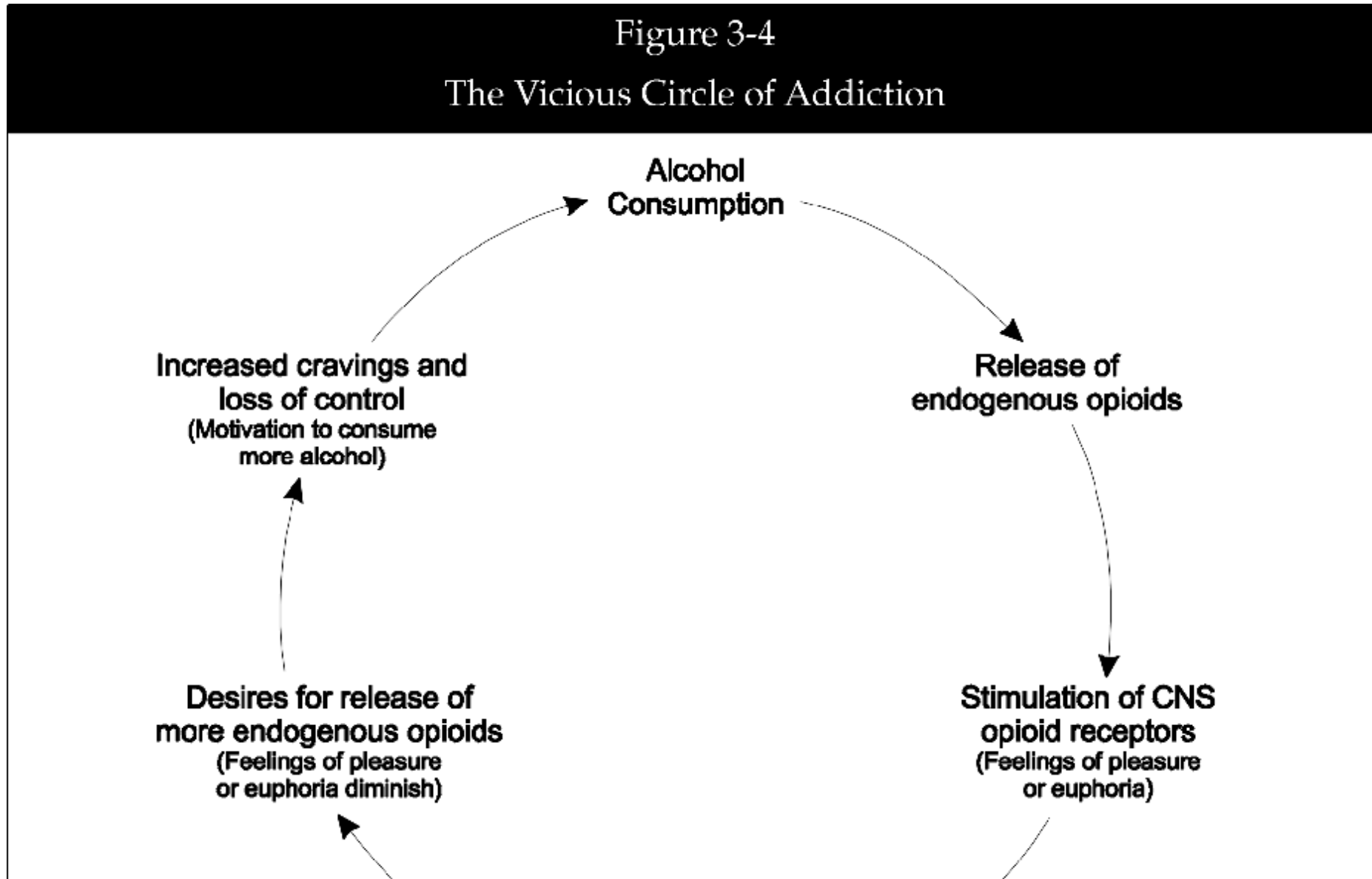
Activiation of
opioidergic/dopaminergic
reward system

Figure 4-1: Outcomes for Naltrexone- and Placebo-Treated Subjects

Figure 4-1 Outcomes for Naltrexone- and Placebo-Treated Subjects		
Outcome	**Naltrexone** ($n = 35$)	**Placebo** ($n = 35$)
Completion rate	69%	60%
Sampled alcohol	46%	57%
Drinking days	1.6%	8.3%
Total relapsing	23%	54%
Relapse among those who "slipped"	50%	95%
Mean craving score at termination (0-9)	1.41	3.42
Source: Volpicelli et al., 1992.		

Figure B-1: The formulary Process and Pharmacoeconomics

Figure B-1

The Formulary Process and Pharmacoeconomics

Formulary addition or
guideline change
request submitted, or
new program instituted

Initial analysis
conducted according to
P&T procedures

Analysis presented to
the P&T
committee

- Primary literature
- Therapeutic review
- Impact on class
- Economic Impact

	THERAPEUTIC	FISCAL
Case 1	Safe and effective. Improvement in current therapy.	Neutral cost impact or cost savings to pharmacy budget.
Case 2	Safe and effective. Improvement in current therapy. May result in operations improvement.	Neutral cost impact or savings to organization's budget (e.g., offset of increase in drug cost by decrease in other costs).
Case 3	Safe and effective. Improvement in current therapy or necessary for new program or therapeutic modality.	New drug or change in therapy results in significant cost increases that cannot be accommodated by pharmacy budget or from resource shifting within the organization's budget. May be justifiable based on organization's mission or plan.

Analysis appears promising —YES→ More detailed fiscal and utilization review performed → Positive results → P&T recommends approval to decision-making authority

Analysis appears promising → NO → STOP

More detailed fiscal and utilization review performed → Negative results → STOP

P&T recommends approval to decision-making authority → Decision approved → Decision published with guidelines for use → 1 year after drug enters formulatory, conduct drug use review
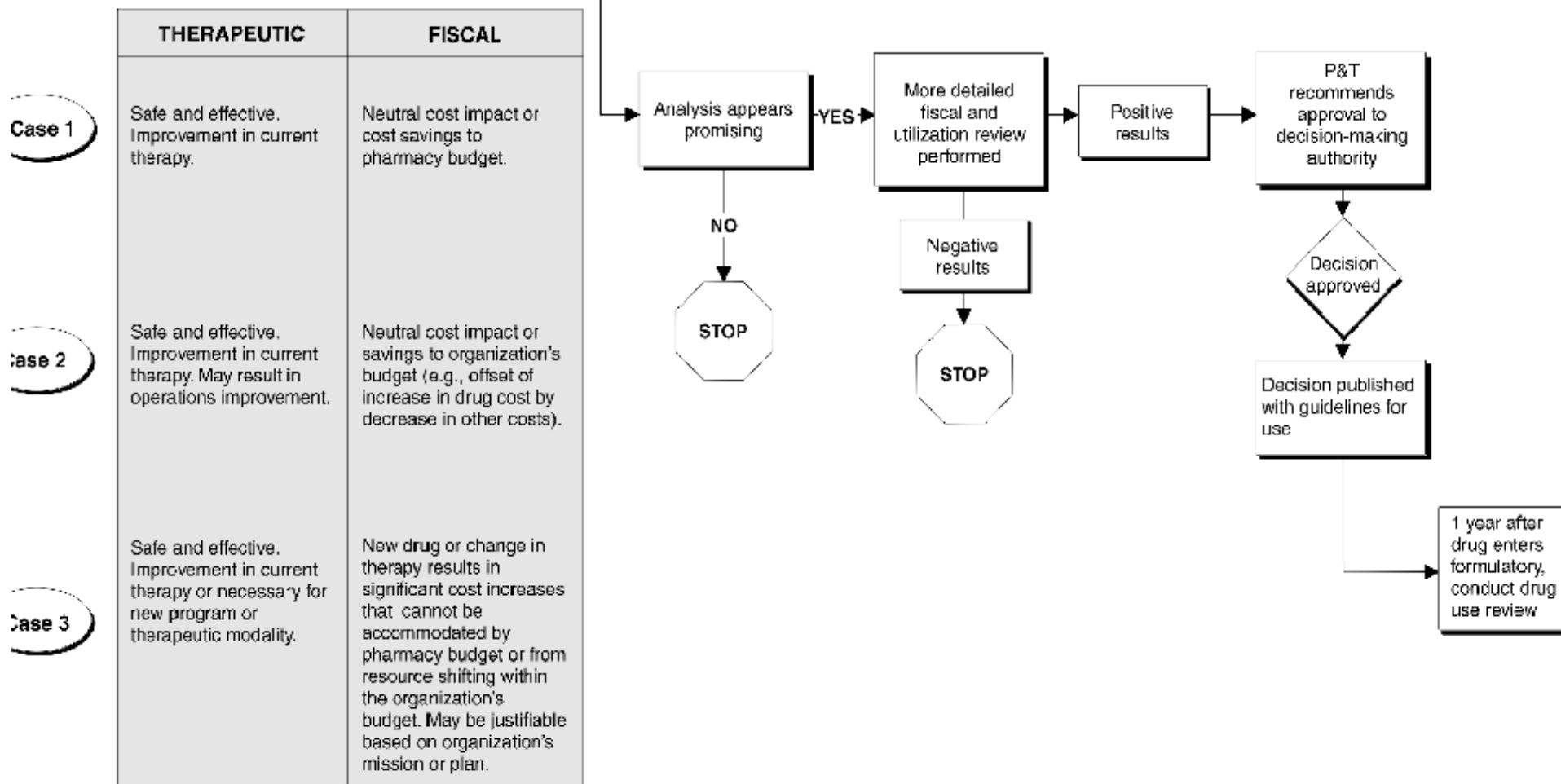
Figure B-2: Federal and Private Web Sites

Figure B-2 Federal and Private Web Sites
Substance Abuse and Mental Health Services Administration (SAMHSA) Sites

- SAMHSA Home Page: http://www.samhsa.gov/
- SAMHSA Weekly Report: http://www.samhsa.gov/wklyrpt.htm
- Managed Behavioral Care Meetings and Conferences: http://www.samhsa.gov/mc/mcmtgs.htm
- Center for Substance Abuse Treatment (CSAT): http://www.samhsa.gov/csat/csat.htm
- Addiction Technology Transfer Centers (ATTC): http://views.vcu.edu/nattc/
- National Evaluation Data and Technical Assistance Center (NEDTAC): http://www.calib.com/nedtac/index.htm
- National Technical Center for Substance Abuse Needs Assessment: http://www.tiac.net/users/ntc/
- CSAT by Fax (A Special Edition of CESARFAX): http://www.health.org/daatpp.htm
- Center for Substance Abuse Prevention (CSAP): http://www.samhsa.gov/csap/index.htm
- Prevline: http://www.health.org/
- National Clearinghouse for Drug and Alcohol Information Online Catalog: http://www.health.org/pubs/catalog/
- Center for Mental Health Services (CMHS): http://www.samhsa.gov/cmhs/cmhs.htm
- The Knowledge Exchange Network (KEN): http://www.mentalhealth.org/

Other Federal Sites

- Department of Health and Human Services (HHS): http://www.os.dhhs.gov:80/
- Healthfinder: http://www.healthfinder.gov/
- HHS Partner Gateway: http://www.os.dhhs.gov:80/partner/
- Drug Enforcement Administration: http://www.usdoj.gov/dea/index.htm
- Food and Drug Administration (FDA): http://www.fda.gov/fdahomepage.html
- Health Care Financing Administration (HCFA): http://www.hcfa.gov/
- Higher Education Center for Alcohol and Other Drug Prevention: http://www.edc.org/hec/
- Justice Information Center (NCJRS): http://www.ncjrs.org/
- Library of Congress: http://lcweb.loc.gov/homepage/lchp.html
- National Institute on Alcohol Abuse and Alcoholism (NIAAA): http://www.niaaa.nih.gov/
- National Institute on Drug Abuse (NIDA): http://www.nida.nih.gov/
- Drug Abuse Warning Network (DAWN): http://www.health.org/pubs/dawn/index.htm
- Monitoring the Future: http://www.isr.umich.edu/src/mtf/index.html
- ONDCP Drugs and Crime Clearinghouse: http://www.ncjrs.org/drgshome.htm
- White House Social Statistics Briefing Room: http://www.whitehouse.gov/fsbr/ssbr.html

Private Sites

- Alcoholics Anonymous World Services: http://www.alcoholics-anonymous.org/
- American Medical Association's Resources on Alcohol and Other Substances: http://www.ama-assn.org/special/aos/resource.htm
- Addiction Research Foundation: http://www.arf.org/
- American Psychiatric Association: http://www.psych.org/

- American Psychological Association: http://www.apa.org/
- American Psychological Association's Addictions Newsletter: http://www.kumc.edu/addictions_newsletter/
- American Society of Addiction Medicine: http://www.asam.org
- Center for Education and Drug Abuse Research (CEDAR): http://www-eval.srv.cis.pitt.edu/~mmv/cedar.html
- Center for Substance Abuse Research (CESAR): http://www.bsos.umd.edu/cesar/cesar.html
- International Certification and Reciprocity Consortium/Alcohol and Other Drug Abuse: http://www.realsolutions.org/icrc.htm
- Internet Alcohol Recovery Center: http://www.med.upenn.edu/recovery
- Join Together Online: http://www.jointogether.org/jtc
- Monitoring the Future: http://www.isr.umich.edu/src/mtf/index.html
- Narcotics Anonymous: http://www.wsoinc.com/basic.htm
- National Association of Alcoholism and Drug Abuse Counselors: http://www.naadac.org/index.html
- National Association of Social Workers (NASW): http://www.naswdc.org
- National Association of State Alcohol and Drug Abuse Directors (NASADAD): http://www.nasadad.org/default.htm
- National Center on Addiction and Substance Abuse (CASA): http://www.casacolumbia.org/home.htm
- National Families in Action (NFIA): http://www.emory.edu/NFIA/
- National Inhalant Prevention Coalition: http://www.inhalants.org/
- National Treatment Consortium, Inc.: http://www.ntc-usa.org/index.html
- Partnership for a Drug-Free America: http://www.drugfreeamerica.org/
- Research Society on Alcoholism (RSA): http://www.sci.sdsu.edu/RSA/
- Research Institute on Addictions: http://www.ria.org/
- The Web of Addictions: http://www.well.com/user/woa/

Figure C-1: Critical Challenges to Effective Use of Research Findings

Figure C-1
Critical Challenges to Effective Use of Research Findings
■ Lack of awareness--potential users do not know about the innovation.
■ Lack of conviction--potential users are not certain that the innovation will work in their setting without unreasonable costs or adverse effects.
■ Lack of resources--potential users may not have access to needed funding, materials, or trained personnel for adopting the innovation.
■ Lack of preparation for change--which can be threatening to staff and difficult to implement, particularly in large and complex organizations.
Source: Adapted from Backer, 1991.

Figure C-2: Characteristics of an Organization That Is Likely to Adopt an Innovation

Figure C-2 **Characteristics of an Organization That Is Likely to Adopt an Innovation**
1. Organizational climate that supports the concept of change, creativity, and innovation through open communication among personnel, with all levels participating in the making of decisions; collegial endorsement of help-seeking and problem-solving; available time for consideration of innovation
2. Organizational size and structure with some emphasis on self-monitoring and assessment to detect troubles, without being too big or too complex for rapid assimilation of change or too bureaucratic, complacent, or conforming to tradition
3. Organizational affluence and capacity that is sufficient to risk innovation and provide the resources for implementing change
4. Leaders in the organization who are attuned to change, politically astute, and respectful of different professional disciplines
5. Professionalism, age, and security of staff members who look forward to innovations; are not threatened by change; and are willing to entertain, discuss, and attempt new procedures or technologies
6. Relationship to the community and the consumer constituency with a demonstrated ability to lead and a capacity for autonomy rather than vulnerability and immediate capitulation to outmoded traditions
Source: Adapted from National Institute of Mental Health, 1971.

***** This Line Follows Each Range of Selected Text *****