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 (leva-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.