NASADAD NATIONAL ASSOCIATION OF STATE ALCOHOL/DRUG ABUSE DIRECTORS

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STATE ISSUE BRIEF NO. 1: Current Alcohol Research in the Use of Medications as an Adjunct to Alcohol Treatment and Implications for State Alcohol Treatment Systems

Background

In an effort to improve the effectiveness of alcohol treatment, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has been conducting and supporting wide ranging research on alcohol abuse and alcohol dependence (alcoholism) including the evaluation of various types of treatment approaches. To more fully understand the relative efficiency and effectiveness of various treatment approaches, they have been compared with respect to the treatment outcomes they produce.

The use of medications as an adjunct to more traditional approaches to treatment has received considerable attention recently because of its promise to improve treatment outcomes (National Institute on Alcohol Abuse and Alcoholism, 2000a). The focus of research in this area is on the development of new medications which reduce alcohol consumption by interfering with the euphoric feeling that occurs while consuming alcohol, and which may reduce the desire to drink after a period of abstinence (Johnson and Ait-Daoud, 1999), (Swift, 1999).

O'Malley et al. (1992), (1996) concluded that psychological treatment and pharmacological treatment strategies are complementary instead of competitive and may be combined effectively to improve treatment outcomes. In an overview of alcoholism treatment in the United States, Fuller and Hiller-Sturmhofel (1999) stated that pharmacotherapy with aversive or anticraving medications may supplement behavioral treatment approaches. The intent of this Brief is to provide State AOD Agency administrators with information which will facilitate decisions around the use of such medications within publicly supported treatment networks. The three major medications under study are naltrexone, nalmefene, and acamprosate.

This is the first of four State Issue Briefs prepared by NASADAD primarily for distribution to State AOD Agencies through support from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). These Briefs are unique in that they are not intended to be a comprehensive review of the science around a topic but rather a compilation of selected findings in an area and an exploration of the implications for administrators of State Alcohol and Other Drug (AOD) treatment systems.

Rationale for Using Medications as an Adjunct to Alcohol Treatment

The major behavioral approaches (nonpharmacological therapies) studied with respect to treatment outcomes include; the

12-step program of Alcoholics Anonymous (AA) which is the most commonly used by far in the treatment of alcoholism; Cognitive Behavioral Therapy which has been studied extensively but rarely used; and Motivation Enhancement Therapy which is a newer treatment tool that is generating great interest in the alcohol field (Fuller and Hiller-Sturmhofel, 1999), (National Institute on Alcohol Abuse and Alcoholism, 2000b). AA is a self-help group that is based on an alcoholic moving through 12 specific steps in the recovery process while attending meetings on a regular basis with other recovering alcoholics. Cognitive Behavioral Therapy helps the client identify external and internal cues or factors that can trigger drinking episodes and develop coping mechanisms to deal with the event. (Internal cues, such as anger, and other mood states, have been found to be better predictors than even the external cues.) Motivation Enhancement Therapy assists the client to become self-motivated to change his/her behavior and encourages continuation of the change process. In a study entitled, "Project Match", it was concluded that while these treatment approaches were effective, there were no significant differences in treatment outcomes between the three approaches. Patient characteristics that might have been predictive of which treatment approach would fit a particular patient were assessed but the study results did not strongly support the predictive measures selected for study (Project Match Research Group, 1997).

In actual practice, many treatment providers utilize a mix of behavioral approaches in a variety of settings. Regardless of approach there is strong and consistent evidence that treatment is effective. In a recent report on treatment effectiveness in State AOD systems, it was shown that treatment is effective regardless of the measure, the indicator area, or the time frame applied (NASADAD, 2001). Fifty-three state treatment outcome studies in 24 states between 1994 to 1999 were reviewed and analyzed using a qualitative meta-analysis approach. In the individual studies, various measures over varying time intervals were recorded from six indicator areas: AOD use, employment status, criminal justice involvement, living arrangement, physical health, and mental health and family/social functioning. Results consistently showed that treatment is effective and beneficial across various settings, populations, and time periods. The real question is, "Can medications, when used in an adjunctive role, produce outcomes substantially better than those achieved by traditional treatment alone?"

The use of medications as an adjunct to alcohol treatment is not a new approach, but new medications are now available and others are in the testing phase that may improve the effectiveness of current behavioral approaches. An early medication, disulfiram (Antabuse) has been available since the late 1940's and is used as an aversive medication which, when taken with alcohol, creates an acutely unpleasant, potentially dangerous physical reaction (Fuller and Hiller-Sturmhofel, 1999). Research support for the use and benefits of using disulfiram has not been strong. Early clinical studies reported that the use of disulfiram improved abstinence rates in recovering alcoholics but methodological problems with those studies have been expressed (Fuller and Roth, 1979). A later large multi-center study using an improved experimental design showed that sustained abstinence rates did not increase among patients as a function of taking disulfiram. However, the study found that abstinence was related to the patient's

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compliance with taking the medication as scheduled (Fuller et al., 1986).

New medications that effect the brain's neurotransmitter systems that are involved in problem drinking are now focusing on reducing the desire to drink and the craving for alcohol. Naltrexone and nalmefene are two medications in the class of opiate antagonists, which act to reduce the "high" or euphoric effect of alcohol. If alcohol is consumed while taking one of these medications, the amount of alcohol consumption should be reduced. In 1994, naltrexone became the first drug approved by the FDA for the treatment of alcoholism in 50 years, although it was previously approved for the treatment of opiate addiction in 1984. Nalmefene is still in the testing phase with human subjects (National Institute on Alcohol Abuse and Alcoholism, 2000a). The approval of naltrexone was based, in part, on the results of two studies in which patients who received psychosocial treatment and naltrexone experienced fewer days of drinking and had reduced relapse to heavy drinking when compared to those patients who received psychosocial treatment alone (Volpicelli et al., 1992), (O'Malley et al., 1992).

Naltrexone and nalmefene … reduce the "high" or euphoric effect of alcohol.

Acamprosate interacts with the glutamate receptors and appears to promote abstinence as well as increased retention. In the United States, acamprosate is currently under review by the FDA as an investigational new drug, although it has been approved and widely used in Europe for the treatment of alcohol dependence. In double blind, placebo-controlled clinical trials with alcoholics, acamprosate significantly increased the rate and duration of abstinence. The safety and efficacy of acamprosate was evaluated in 16 controlled clinical trials involving more than 4,500 patients across 11 European countries. In 14 of the 16 studies it was found that patients using acamprosate had a significantly greater rate of treatment completion, time to first drink, abstinence rate, and/or cumulative abstinence duration than patients receiving a placebo (Mason and Ownby, 2000).

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A promising approach to the treatment of alcoholism may be one in which medications such as naltrexone and acamprosate are combined and used as a pharmacological adjunct to behavioral treatment. NIAAA is currently conducting a study called "Project COMBINE" to evaluate combinations of pharmacological and behavioral interventions. Use of these medications in combination may enhance their effectiveness as an adjunct to behavioral therapies in alcohol treatment (Swift, 1999), (National Institute on Alcohol Abuse and Alcoholism, 2001a).

The COMBINE study will involve 1,375 participants who meet criteria for alcohol dependence across 11 treatment research centers over a 24-month period. Participants will receive either a moderate or low intensity behavioral treatment, and either naltrexone alone, acamprosate alone, a combination of naltrexone and acamprosate, or a placebo. There will be four months of structured outpatient treatment and three follow up visits over the subsequent 12 months (National Institute on Alcohol on Alcohol Abuse and Alcoholism, 2001b).

The last group of medications that have been studied and considered for use in alcohol treatment are the Selective Serotonin Reuptake Inhibitors (SSRIs) (Pettinati et al., 2001). These medications have been

evaluated with respect to their ability to reduce alcohol consumption in depressed individuals with alcohol dependence and have yielded inconsistent results. One such medication, fluoxetine (Prozac) has been found to be effective in treating alcoholics with co-occurring psychiatric disorders such as major depression. Cornelius et al. (1997) found that depressive symptoms decreased, and alcohol consumption decreased significantly in patients who were taking fluoxetine compared to those who were taking a placebo. In another study, Pettinati et al. (2001) found that another SSRI, sertraline helped alcohol dependent patients without lifetime depression reduce their drinking, but sertraline was no better than the placebo for patients with co-morbid depression. It appears that SSRIs may work with certain types of depressed individuals with certain types of alcoholics, but their efficacy in the treatment of alcohol dependent patients is still uncertain and further research is needed to identify those patients who are most likely to benefit from this type of medication.

Brief Summary of Research Results on Naltrexone, Nalmefene, and Acamprosate

Naltrexone

Many studies have been conducted to examine the effects of naltrexone on alcohol consumption and treatment outcomes (National Institute on Alcohol Abuse and Alcoholism, 2000a). One study showed that patients who took naltrexone experienced less euphoria from drinking than patients taking a placebo (Volpicelli et al., 1995). In two other studies, when social drinkers in a laboratory setting took naltrexone, they indicated that they experienced sluggish and sedative effects of the alcohol rather than stimulative effects (Swift, 1995), (Swift et al. 1994). Studies by Volpicelli et al., (1992) and O'Malley et al. (1992) demonstrated that patients receiving naltrexone, regardless of racial, ethnic and economic differences and varying levels (types and intensities) of behavioral treatments, drank less frequently, and consumed less alcohol when they did drink. In a later study, O'Malley et. al., (1995) reexamined data from the two previously mentioned studies and found that patients who returned to drinking refrained from drinking for a longer period of time and delayed their first episode of heavy drinking when naltrexone was taken compared to patients who took a placebo. Among the patients who returned to drinking, those using naltrexone compared to the placebo-treated patients drank less frequently, on a significantly smaller percentage of days, and were less likely to relapse to heavy drinking.

There are important issues associated with the actual patient use of naltrexone that have been examined in a number of studies. These include issues such as compliance, dosage, side effects, cost and candidate selection. The construction of an overall treatment program must accommodate these individual considerations (Johnson and Ait-Daoud, 1999). The practical effectiveness of naltrexone is based on patient compliance with medication instructions and schedules. Volpicelli et al., (1997) indicated that naltrexone was effective in decreasing relapse to heavy drinking for patients who completed a 12-week course of treatment and took their medication as prescribed. Differences were measured in percentage of drinking days for those patients who took their pills correctly compared to those patients who did not comply with medication instructions. In another large multicenter study (Chick et al., 2000), naltrexone was found to be effective in conjunction with psychosocial therapy in alcohol dependent patients who comply with treatment.

Determining the optimal, patient specific dosage for naltrexone may improve its

overall efficacy. McCaul et al. (2000) varied the dose (0, 50 and 100 mg) of naltrexone in an effort to examine the interactions of naltrexone and alcohol dosage levels to determine optimal dosage. The typical dose is 50 mgs per day, however increasing the dosage to 100-150 mgs may be more effective in patients who don't show success at the lower dosage. At 50 mg dosage, no serious side effects have been found, with nausea being the most common side effect during the use of naltrexone (Croop et al., 1995). At very high doses (300 mg), naltrexone may be associated with adverse liver effects.

Follow up studies could be helpful in determining how long the medications should be taken to fully exploit its potential effectiveness (National Institute on Alcohol Abuse and Alcoholism, 2000a). Usually, naltrexone is administered in studies over a 12-week treatment period (O'Malley et al., 1992), (Monti et al., 2001), (Chick et al., 2000). Monti et al. (2001) evaluated the effects of naltrexone compared with a placebo for a 12-week period after patients received coping skills and communications skills training. Drinking outcomes were assessed at 3, 6, and 12 months after discharge. Patients who were compliant in taking their medication and received naltrexone compared to the placebo had significantly fewer heavy drinking days and fewer drinks on days they drank during the treatment period but not during the subsequent 9 months. These results suggest that it may be beneficial to extend the treatment period.

Identifying and selecting candidates that could benefit the most from the use of naltrexone and who would be most likely to comply with a recommended dosage schedule would be a practical and cost-effective strategy since the cost of naltrexone is significant. (Costs range from $2.50 to $4.43/day/dose.) The selection process for identifying the most suitable candidates to receive naltrexone and the appropriate duration of use for different treatment groups is yet to be determined. Some patients may respond well to an initial treatment of 12 weeks with naltrexone and remain abstinent, but may need to initiate treatment again for short periods of time to avoid a relapse (National Institute on Alcohol Abuse and Alcoholism, 2000a).

Nalmefene

Nalmefene is a newer opiate antagonist that has not yet been approved by the FDA for alcohol treatment. It is similar in structure to naltrexone and similar in its actions (interferes with the euphoric effects of alcohol consumption) (National Institute on Alcohol Abuse and Alcoholism, 2000a). However, it has less potential for toxic effects on the liver. In a study in which patients were randomly assigned to either a group that would receive nalmefene or a group that would receive a placebo during a twelve-week treatment period, the patients who received nalmefene were 2.4 times less likely to relapse to heavy drinking when compared to those who received a placebo during the treatment period. Patients were administered varying doses, had high compliance rates, and experienced no adverse side effects (Mason et al., 1999). This drug may serve as a good alternative to naltrexone if a patient does not respond to or is intolerant of naltrexone.

Acamprosate

In Europe, acamprosate has been available since 1989 and has been used to treat alcohol dependence in many countries, although it is still being analyzed for safety and efficacy in the United States (Mason and Goodman, 1997). Acamprosate is different from the opioid antagonists in that it affects the glutamate neurotransmitter system. (National Institute on Alcohol Abuse and Alcoholism, 2000a). Mason and Ownby (2000) reviewed 16 double-blind

placebo-controlled clinical trials in 11 European countries. In a French study, two doses of acamprosate, 1.2 grams and 2 grams a day, and a placebo were administered to subjects. It was found that the higher doses significantly increased the proportion of subjects who remained abstinent at 6 and 12 months and reduced craving at 3 months (Paille et al., 1995). Many other studies support the increase in abstinence rates when acamprosate is used compared to a placebo (Sass et al., 1996), (Whitworth et al., 1996), (Geerlings et al., 1997). Finally, there is no evidence of drug interactions between alcohol, other alcohol medications, and other medications used to treat mental illness such as depression (Durbin et al., 1996). Also, it should be noted that since acamprosate is not metabolized to a large degree in the liver, patients with liver problems could use acamprosate instead of naltrexone. (Wilde and Wagstaff, 1997).

Implications for Alcohol Treatment in State Systems

Using new medications as an adjunct to alcohol treatment in the State AOD systems holds promise for improving overall treatment outcomes and could significantly change the way alcohol dependence is treated. Currently, the use of medications as an adjunct to alcohol treatment is not widely used in State AOD Agency supported facilities. In many cases, the existing system for alcohol treatment would need to be modified to incorporate the delivery of medications to clients that may benefit from not only counseling for alcohol dependence, but also from taking medications (National Institute on Alcohol Abuse and Alcoholism, 2001a). To support the broader use of medications in alcohol treatment, physicians not currently associated with treatment facilities would need to be identified, new operational procedures for communicating with them may need to be developed, and issues concerning the best approach for applying the medications on a systemic basis would need to be addressed.

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In this last section, issues related to introducing the use of medications as an adjunct to alcohol treatment in the State systems are presented and areas that need further study are noted.

Issues and Considerations for Using Medications as an Adjunct to Alcohol Treatment in the State AOD System

Client Screening and Assessment Instruments – Both physicians and counselors are in need of tools to determine which clients with alcohol disorders would most benefit from the use of medications as an adjunct to alcohol treatment. These instruments should also help to identify those clients who are motivated to use medications as prescribed.

Professional Networking – It is anticipated that the medications under discussion will be prescribed with increasing frequency by primary care and other physicians. At the present time few linkages exist that would permit prescribing physicians to access components of traditional alcoholism treatment. Mechanisms to ensure the provision of comprehensive and coordinated care are required. The availability of effective medications for the treatment of alcohol disorders also provides a natural role for physicians' involvement in interventions. The New York model hospital-based intervention process, for example, could be easily modified to incorporate the use of medications.

Medication Monitoring Requirements – Naltrexone, in very high doses (300 mg), can adversely effect the liver. Some patients are intolerant of naltrexone and experience nausea if given in the initial stages of recovery in which case nalmefene might be a good alternative to naltrexone. Acamprosate does not appear to have the same adverse effect since it is not metabolized by the liver, and does not appear to have drug interactions between alcohol, other alcohol medications and other medications to treat mental illness. This information is supported by the research noted earlier in this report. It should also be mentioned that naltrexone should not be used with clients receiving opiates because it will trigger the withdrawal process (National Institute on Alcohol and Alcoholism Workshop, 2001a).

Cost of Medication - The cost of medication such as naltrexone in the use of alcohol treatment could be a financial burden for many clients for whom medications for alcohol treatment are not covered under their insurance plan. Cost could also be a factor among both the uninsured and the underinsured. Obtaining these medications could be problematic for Medicaid recipients if the medications are not included in a State's Medicaid formulary. For the studied courses of treatment, naltrexone was most frequently prescribed for 12-week periods with one 50 mg dose per day. Cost per client treatment episode would fall between $210 and $372.

Cost Offset Potential – Prescription drug expenditures were only .03 percent of substance abuse treatment expenditures in 1997 as compared to .01 percent in l987 (Coffey et. al, 2000). It is possible that using medications as an adjunct to alcohol counseling in the treatment of alcoholism could increase overall treatment effectiveness and as a result reduce overall long term costs of both substance abuse treatment services and related societal costs. Once medications have been successfully introduced and widely used, studies addressing the cost offset issue should be conducted.

Potential for Abuse – Naltrexone has no substantive history of abuse, is not a controlled substance (Amera-Chem, 2001), and may be prescribed by any licensed physician.

Potential for Diversion – Given the minimal record of abuse, there is almost no diversion potential for naltrexone.

Special Concerns – Use of medications as an adjunct to alcohol treatment ought to be considered but the use of medications alone, or in place of counseling and other services, is discouraged. Approaches for discouraging the use of medications without counseling to treat alcoholism need to be developed and promoted. Naltrexone should not be used for alcohol dependence when a patient is also dependent on any opiates because of the risk of precipitating opiate withdrawal. It should also not be given to patients who may have an anticipated need for opiates within the near future.

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Evaluation Process – After a practical approach for the broad use of medications as an adjunct to alcohol treatment is developed and implemented in the public AOD system, the value of using medications as measured by treatment outcomes could be assessed. Two important questions need to be asked. Are clients benefiting from the introduction of medications as an adjunct to alcohol treatment? What adjustments or modifications can be made to improve or enhance the approach used and increase

treatment effectiveness? The State AOD Agencies constitute multiple natural laboratories that could assist NIAAA in satisfying this need.

Need for More Research on the Practical Issues and Approaches Concerning the Use of Medications as an Adjunct to Alcohol Treatment

There is a need for NIAAA to conduct further research in candidate selection, usage and dosage questions, and evaluation of medications in the public AOD treatment delivery system as described below:

- Develop processes for identifying the most suitable candidates for treatment with medications. These processes might include refined assessment instruments, corroborating biological markers, and developing patient management guidelines, etc.
- Address usage issues such as when should a medication be used, which medication should be used or what combination of medications should be used, what is the best time frame for use, and what is the best dose for specific patient groupings. Answers to these questions could be sought in collaboration with AOD Directors and the provider networks.
- Evaluate the process for delivering medications, monitoring compliance, and assessing treatment outcomes so that adjustments to the treatment delivery system can be made as needed to improve the overall system.

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NASADAD is a private not-for-profit educational, scientific, and informational organization that was established in Washington D.C. in 1971 to represent Directors of State Alcohol and Drug Abuse Agencies. NASADAD's basic purpose is to foster and support the development of effective alcohol and other drug abuse prevention and treatment programs throughout every State. NASADAD serves as a focal point for the examination of alcohol and other drug related issues of common interest for both State and Federal Agencies.

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