Pharmacotherapy for Alcohol Dependence

Summary

Under its [Evidence-Based Practice Program](), the Agency for Health Care Policy and Research (AHCPR) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools. Contractor institutions review all relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities.

Overview

The pharmacotherapy for alcohol dependence was selected as an evidence report topic by the Agency for Health Care Policy and Research (AHCPR) because of its timeliness, the severity and impact of the disease, and the need for careful evaluation of new therapeutic modalities for its treatment. Alcoholism is a prevalent disease that will affect on the order of 10 percent of the adult population of the United States. An estimated 100,000 Americans die each year from alcohol-related disease or injury. The serious financial and nonfinancial impact of this disease extends to family members and society in general, and its annual dollar cost to the country has been estimated (as of 1995) to exceed $166 billion.

The treatment of alcohol dependence requires a two-step approach that includes withdrawal and detoxification followed by further interventions to maintain abstinence. There is considerable uncertainty about the best treatment strategies for patients in the post-detoxification stage. Some advocate a "drug-free" 12-step approach developed by Alcoholics Anonymous (AA), while others assert that the 12-step approach or other psychosocial approaches combined with appropriate nonaddictive pharmacotherapies may improve treatment outcomes.

Reporting the Evidence

This summary is drawn from an evidence report that focuses on the pharmacotherapies used for the treatment of alcohol dependence. The report is organized around a series of major clinical questions on the pharmacotherapy for alcohol dependence. They involve pharmaceutical agents that have been historically or are presently used in the treatment of alcoholism: disulfiram, the opiate antagonists naltrexone and nalmefene, serotonergic

agents such as ondansetron, buspirone, and the selective serotonin reuptake inhibitors (SSRIs, such as citalopram, fluoxetine, paroxetine, sertraline, etc.), and lithium. Disulfiram and naltrexone, in particular, are mainstream agents in use in the United States today. However, it is important to recognize that the field of pharmacotherapy for alcohol dependence has evolved substantially over the past 5 years, especially with the emergence of data on the opiate antagonists.

Concomitantly, there is one promising pharmaceutical agent currently in use in Europe—acamprosate (calcium acetyl homotaurinate)—for preventing alcohol relapse. An investigational new drug (IND) application is on file for this drug at the United States Food and Drug Administration (FDA), and it is in Phase III trials in this country.

Much of the literature examined for the evidence report was designed to establish efficacy: Does the medication reduce alcohol intake in a well-controlled study setting? Examination of potential harms associated with treatment is equally important. The evidence on treatment harms was sometimes found within randomized controlled trials (RCTs) but was also identified through prospective cohort studies or secondary data sources, although the latter sources were not systematically searched.

Key Clinical Questions

Five questions were addressed relevant to the pharmacotherapy for treating the core symptoms of alcohol dependence such as craving, loss of control (relapse), abstinence, and total drinking or nondrinking days. The first three questions relate to three agents used primarily for the treatment of alcohol dependence: disulfiram, the opiate antagonists naltrexone and nalmefene, and acamprosate. These agents have been in use for different periods of time, and the amount of evidence available for each agent differs substantially.

Disulfiram inhibits aldehyde dehydrogenase and leads to increased levels of acetaldehyde when alcohol is consumed, with subsequent adverse physical effects such as nausea, headache, and weakness. Disulfiram has been in use for approximately 50 years. The opiate antagonists (naltrexone and nalmefene), which block opioid receptors leading to a hypothesized reduction in the rewarding properties of alcohol, have been in use in the United States for only a few years. Acamprosate, whose mechanism of action has not been clearly established as yet, is not available in the United States but has been used in Europe for a few years. The first three questions are:

> 1. What is the efficacy of disulfiram relative to placebo in treating alcohol dependence?
> 2. What is the efficacy of naltrexone relative to placebo in treating alcohol dependence?
> 3. What is the efficacy of acamprosate relative to placebo in treating alcohol dependence?

The fourth and fifth questions relate to drugs that have been approved by the FDA for conditions other than alcohol dependence such as depression and bipolar disease:

> 4. What is the efficacy of serotonergic agents relative to placebo in the treatment of alcohol dependence?
> 5. What is the efficacy of lithium relative to placebo in the treatment of alcohol dependence?

Animal studies indicate that alcohol intake can be reduced by SSRIs and other serotonergic agents such as buspirone and ondansetron. A moderate literature has examined the efficacy of these agents in maintaining remission in humans.

Finally, lithium has been used to treat alcoholism. Lithium has been a mainstay of treatment for bipolar affective disorder, although the literature in the area of alcohol dependence is limited. Nonetheless, clinical issues remain.

The efficacy of each of these agents was determined by an assessment of the following factors: reduction in the number of standard drinks of alcohol, reduction in the number of drinking days (or increase in the number of nondrinking days), reduction in relapse rates defined as time to first drink or development of an a priori defined relapse, overall resumption of drinking over the course of the study, number of episodes of heavy drinking, severity of side effects, and compliance with drug therapy.

Multiple other agents have been used to assist in the maintenance of remission from active drinking. These include agents that directly affect brain dopaminergic systems (bromocriptine) or gamma-amino butyric acid (GABA) systems (gamma-hydroxy butyrate). Evaluating the role of all agents that have been tried in the treatment of alcohol dependence would be of interest to the alcohol treatment professional but is outside the scope of the evidence report.

Methodology

The research methodology used in developing the evidence report is summarized here, including the inclusion and exclusion criteria for the literature search, the Medical Subject Headings (MeSH) used, the databases searched, and the data abstraction process. Procedures used for assessing quality and grading the evidence and development of evidence tables and supplemental analyses are also briefly discussed.

Inclusion and Exclusion Criteria for the Literature Search

The inclusion criteria were related to the population being studied, the treatment setting for patients with alcohol dependence, the countries where these studies typically are done, and the publication languages. The inclusion criteria were:

1. Publication from 1966 through November 1997 in English, French, or German.
2. Adult subjects, 18 years of age or older, with alcohol dependence.
3. Sample sizes of 10 or more subjects.
4. Use of a control group for comparison.

Reviews, letters to the editor, and studies that did not address the efficacy of the key therapies were excluded.

The MeSH terms used for the search included the key therapies (disulfiram, the opiate antagonists [naltrexone and nalmefene], acamprosate, serotonergic agents such as ondansetron, buspirone, and the selective serotonin reuptake inhibitors [SSRIs], and lithium), alcoholism, alcohol drinking, study characteristics, and study design. The project librarian defined study characteristics and study design before using them in the

search. An extensive gray literature search also was conducted to identify symposia proceedings, industry reports, and unpublished documents that contained efficacy data.

The search used the "explode" function, which includes all the individual brand and generic drug names without the need to list all the names separately. Because "alcohol dependence" does not have its own MeSH entry, the terms "alcoholism" and "alcohol drinking" were used. In this search, "study characteristics" included: analytic studies, case-control studies, retrospective studies, cohort studies, longitudinal studies, followup studies, prospective studies, cross-sectional studies, clinical protocols, clinical trials (phases I-IV), controlled clinical trials, RCTs, intervention studies, and sampling studies. "Study design" included: cross-over studies, double-blind method, matched pair analysis, meta-analysis, random allocation, reproducibility of results, and sample size.

The searches were conducted in MEDLINE[R], HealthSTAR, the American Society of Health-System Pharmacists' International Pharmaceutical Abstracts database, EMBASE, Alcohol and Alcohol Problems Database, and PsycINFO[R]. Materials available from the Cochrane Collaboration and the National Health Service Centre for Reviews and Dissemination were also reviewed.

An extensive search of the gray literature was conducted to identify literature from nontraditional sources including:

- Government documents and monographs.
- Industry reports and publications.
- Unpublished studies and works in progress.
- Review of tables of contents from symposia proceedings.
- FDA Medical Officer Reviews of efficacy data.

Data Abstraction Process

Four detailed data extraction forms were developed for entry of relevant information from the efficacy publications: the primary Data Extraction Form, Followup Results Form, Comorbid Study Results Form, and the Adverse Events Form.

These forms were pretested several times before use. An Extraction Guide was developed for use during the formal training session and as a reference guide during the extraction process. A dual abstraction method was employed using a content reviewer and a method reviewer. The content reviewers had been trained in the basic sciences, understanding the effects of alcohol on animals. The method reviewers had been more generally trained in qualitative and quantitative methods such as epidemiology, economics, and statistics. The abstraction process was monitored by the project's task leader and scientific director, reviewing the forms for consistency and providing feedback as necessary. Because of the complexities in the topic area being reviewed, the task leader and scientific director chose to conduct a third conflict-resolution review of each article. The review of harms data was limited; thus a formal and extensive harms review was not conducted.

Assessment of Article Quality and Grading of the Evidence

To assess the quality of the articles from the design, analysis, and reporting perspectives, a quality rating form was developed and included as the last two pages of the Data Extraction Form. It was used to evaluate, among other factors, the study design, diagnostic and outcome measurements, statistical analyses, and the discussion of the reviewed articles. The form was based on questions that summed to 40 points and were then scaled to 100 points. Besides evaluating the quality of the articles, grades were assigned for the evidence. Two grades were provided, one for efficacy and another for harms. The grades for efficacy were based on the adequacy of the data (i.e., consistency, quality, sample size, and magnitude of effects). For harms, the seriousness of the side effect, whether it was a known or an unexpected side effect of the therapy, and its frequency compared with placebo were considered. The grades were defined as follows:

Efficacy data grades:

- Good (A): Data are sufficient for evaluating efficacy. The sample size is adequate. The data are consistent and indicate that the key drug is clearly superior to placebo for treating alcohol dependence.
- Fair (B): Data are sufficient for evaluating efficacy. The sample size is adequate. The data indicate that inconsistencies in the findings for the alcohol outcomes between the key therapy and placebo are such that the efficacy of the key therapy for treating alcohol dependence is not clearly established.
- Poor (C): Data are sufficient for evaluating efficacy. The sample size is adequate. The data show that the key therapy is no more efficacious for treating alcohol dependance than placebo.
- Incomplete evidence (I): Data are insufficient for assessing the efficacy of the key therapy for treating alcohol dependence based on limited sample size or poor methodology.

Harms data grades:

- Low: The side effects are not life-threatening; those reported are known side effects of the therapy.
- High: A life-threatening side effect; it is serious and its frequency of occurrence is greater in the key therapy group than in the placebo group.

Evidence Table Development and Supplemental Analyses

Two separate evidence tables (study design and study outcomes) were developed for each key therapy evaluated. Several different variables are used in the alcohol literature to assess return to drinking. Although a meta-analysis comparing each of the key therapies for one or more outcome variables would have been useful for treatment providers, the data were not available for this type of analysis at this time.

Findings

Findings are presented in bullet format for the five major drugs or drug classes reviewed.

Disulfiram

- A substantial literature has been generated on the use of disulfiram in alcoholism, but the number of controlled clinical trials is limited.
- Controlled clinical trials of disulfiram reveal mixed findings. There is little evidence that disulfiram enhances abstinence, but there is evidence that disulfiram reduces drinking days. When measured, compliance is a strong predictor of outcome.
- Studies of disulfiram implants are methodologically weak and generally without good evidence of bioavailability.
- Studies of supervised disulfiram administration are provocative but limited.

Naltrexone

- Trials of naltrexone in the treatment of alcoholism are recent and of generally good quality.
- There is good evidence that naltrexone reduces relapse and number of drinking days in alcohol-dependent subjects.
- There is some evidence that naltrexone reduces craving and enhances abstinence in alcohol-dependent subjects.
- There is good evidence that naltrexone has a favorable harms profile.

Acamprosate

- Trials of acamprosate in alcohol dependence are large but limited to European populations.
- There is good evidence that acamprosate enhances abstinence and reduces drinking days in alcohol-dependent subjects.
- There is minimal evidence on the effects of acamprosate on craving or rates of severe relapse in alcohol-dependent subjects.
- There is good evidence that acamprosate is reasonably well tolerated and without serious harms.

Serotonergic Agents

- There are several controlled clinical trials of serotonergic agents in primary alcoholics without comorbid mood or anxiety disorders.
- There is minimal evidence on the efficacy of serotonergic agents for treatment of the core symptoms of alcohol dependence.
- There is some evidence on the efficacy of serotonergic agents for the treatment of alcohol-dependent symptoms in patients with comorbid mood or anxiety disorders, although the data are limited.

Lithium

- There are limited studies on the effects of lithium in primary alcoholics without comorbid mood disorders.
- There is evidence that lithium is not efficacious in the treatment of the core symptoms of alcohol dependence.

- There is minimal evidence for efficacy of lithium for the treatment of alcohol-dependent symptoms in patients with comorbid depression.

Future Research

Although the quality of the research on pharmacotherapies for alcohol dependence has improved substantially since the 1960s, numerous difficulties were encountered in developing the evidence report. These difficulties involved both reviewing the available literature and developing concrete conclusions or drawing appropriate inferences about the efficacy of these drugs in treating the different patient populations suffering from alcoholism. To address some of these drawbacks and deficiencies in the empirical knowledge base, several significant areas have been identified for attention in future research. The topics and/or methodologic issues deserving high priority include:

- Pharmacotherapies shown to have efficacy in the treatment of alcoholism should be studied over longer time periods to establish their efficacy as maintenance treatments. These trials should probably last several years. Extending the length of followup once active treatment has ended, perhaps as long as 5 to 10 years, would also provide information on whether efficacy is still evident beyond active treatment. Lack of efficacy beyond active treatment would then raise the question of the value of very-long-term maintenance.
- Combination therapies, i.e., therapeutic regimens that involve two or more medications given simultaneously, should be examined for efficacy.
- Psychosocial co-interventions used within pharmacotherapy trials require more standardization, better compliance assessment, and better reporting in future publications. These include psychosocial interventions provided outside specialized treatment programs and in primary care settings.
- Effectiveness studies are needed to establish the benefit of these treatments in various settings (i.e., outside the specialized centers typically used in RCTs to date and, by implication, in patient populations encountered in all types of settings) once efficacy for alcohol dependence has been established.
- Common outcome measures need to be determined by standardizing the definition of outcomes and how they are assessed and using broader sets of endpoints that include clinical and health-related quality-of-life indicators.
- High dropout rates warrant attention, including identifying reasons for (differential) dropout, improving the reporting of baseline characteristics of different groups, and designing innovative ways to overcome significant dropout, especially for long-term studies.
- Research on the pharmacokinetics of these medications includes evaluating the relationship of drug blood levels and of drug metabolites to therapeutic or toxic outcome.
- All RCTs should include pharmacotherapy compliance assessment and enhancement for all treatment groups.
- The relationship of pharmacotherapy to patient heterogeneity needs to be better understood, including effects related to the patient's sex, severity of dependence, co-existing mental disorders, and the interactions among these factors.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Health Care Policy and Research by the Research Triangle Institute (RTI) and the University of North Carolina (UNC) at Chapel Hill, under contract No. 290-97-0011. It is expected to be available in early 1999. At that time, printed copies may be obtained free of charge from the AHCPR Publications Clearinghouse by calling 1-800-358-9295. Requesters should ask for Evidence Report/Technology Assessment Number 3, *Pharmacotherapy for Alcohol Dependence* (AHCPR Publication No. 99-E004). When available online, the Evidence Report will be at: http://www.ahcpr.gov/clinic/index.html#evidence.

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