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REVIEW SERIES

A SYSTEMATIC REVIEW OF OPIOID ANTAGONISTS FOR ALCOHOL DEPENDENCE

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ABSTRACT

The results from animal studies suggest that opioid antagonists may prevent the reinforcing effects of alcohol consumption. This systematic review was carried out to determine the effectiveness of opioid antagonists for attenuating or preventing the recommencement of alcohol consumption in patients with alcohol dependence. Electronic searches of MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register were undertaken. Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. The reference lists of the identified papers were also examined. All relevant randomized controlled trials (RCTs) and clinical control trials (CCTs) were included. Participants were people with alcohol dependence, diagnosed by any set of criteria, except, alcohol dependence with currently abstinent. Naltrexone (NTX), nalmefene (NMF), and other opioid antagonists with/without other biological or psychosocial treatments were examined. A variety of clinical outcomes, for example alcohol consumption, duration of abstinence, were considered. The dichotomous data were extracted on an intention-to-treat basis. The Peto Odds Ratio was used to assess the dichotomous data. The Weighted Mean Difference was used to assess the continuous data. The results indicate that the short-term (< 3 months) benefits of NTX were shown in three respects, which were number of patients who return to drinking, percentage or number of drinking days and the number of standard drinks of alcohol. However, 6 months after the completion of 12-week NTX treatment, the benefit of decreasing the number of patients who return to drinking were lost. The evidence from small sample-size studies suggested that disulfiram and NTX plus an aversive agent were more effective than NTX in some respects. From two short-term and small sample-size studies, the benefit of NMF was shown only in the respect of number of patients who return to drinking. The limited evidence suggests that NTX has some benefits for patients with alcohol dependence, but patients' adherence to treatment should be of concern. Psychosocial treatments should be concurrently given with NTX. The optimal duration of NTX treatment is not yet known. Due to the dearth of evidence, at present, the combination of NTX and disulfiram or NMF alone should not be used in everyday clinical practice.

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INTRODUCTION

RATIONALE FOR THE SYSTEMATIC REVIEW OF OPIOID ANTAGONISTS FOR ALCOHOL DEPENDENCE

Healthcare providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information. Systematic review is an application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. High quality systematic reviews can provide a basis for rational decision making. Meta-analysis, the use of statistical methods to summarize the results of independent studies, can provide more precise estimates of the effects of healthcare those derived from the individual studies included in a review. The need for systematic reviews of healthcare has grown rapidly and continues to grow, as reflected by the number of articles about review methods and empirical studies of the methods used in reviews, the number of systematic reviews published in healthcare journals, and the rapid growth of the Cochrane Collaboration.

The Cochrane Collaboration is a not-for-profit organization that aims to help people make well-informed decisions about healthcare by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Cochrane reviews (the principal output of the Collaboration) are published electronically in successive issues of *The Cochrane Database of Systematic Reviews*.

Because of the high prevalence of alcohol dependence and its social, psychological, and physical morbidity, a systematic review of treatment for alcohol dependence is needed. As opioid antagonists, for example naltrexone (NTX), is a new technology for the treatment of alcohol dependence, a systematic review in this issue would be of helpful for healthcare providers, consumers, researchers, and policy makers in making a clinical judgment.

This systematic review was conducted by using the Cochrane Collaboration standards. An electronic version of this report will be published as a Cochrane Review and will be updated as the new evidence emerges.

ALCOHOL DEPENDENCE, ITS PHARMACOLOGICAL TREATMENT, AND OPIOID ANTAGONISTS

Alcohol dependence is a prevalent psychiatric disorder. Its 1-year and lifetime prevalence rates are about 7% and 14% of general population, respectively (Regier 1993, Kessler 1994). Its health, social, and economic consequences are usually devastating. Although many individuals do achieve long-term sobriety with treatment, others continue to relapse and deteriorate despite multiple courses of treatment.

Since psychosocial treatment programs for alcohol dependence have had only limited success, several pharmacological agents for treating this problem have been studied.

Many pharmacological adjuncts to alcohol rehabilitation treatment programs have been investigated. For example, disulfiram, lithium, selective serotonin reuptake inhibitors (SSRIs), and acamprosate have been investigated. Disulfiram has been shown to have limited clinical utility. Highly motivated alcohol-dependent patients taking disulfiram may partially improve in some respects, e.g., drinking frequency, amount of alcohol consumption (Garbutt 1999). While the results of some studies showed that lithium reduced drinking in alcohol-dependent patients with mood disorders (Merry 1976; Fawcett 1984), a randomized controlled trial failed to demonstrate any benefit for lithium in either depressed or non depressed patients (Dorus 1989). The efficacy of SSRIs in alcohol-dependent patients remains to be tested in randomized, double-blind studies with large sample sizes. Acramprosate is considered to be an effective treatment for attenuating alcohol consumption (Garbutt 1999).

While the results of many studies have suggested that opioid agonists increase alcohol consumption, others have shown that mu-opioid antagonists and partial agonists reduce alcohol consumption (Volpicelli 1986; George 1991).

No current theoretical model explains how endogenous opioids and opiate antagonists are related to alcohol consumption. However, studies conducted in both rodents and monkeys have demonstrated that naloxone and naltrexone (NTX) attenuate voluntary self-administration of alcohol and stress-induced increases in alcohol consumption. This suggests that these agents may prevent the reinforcing effects of alcohol consumption (O'Brien 1996).

Based on the results of these animal studies, opioid antagonists such as NTX and nalmefene (NMF) have been studied to determine their benefits in treating alcohol dependence.

OBJECTIVES

To determine the relative effectiveness of opioid antagonists in comparison to placebo, other medications, and psychosocial treatments for attenuating or preventing the recommencement of alcohol consumption in people with alcohol dependence. In addition, discontinuation rate, mortality, patient satisfaction, degree of functioning, health-related quality of life, and economic outcomes were also evaluated.

METHODS

SEARCH STRATEGY

Electronic searches:

The searches of MEDLINE (1966 – May 1999), EMBASE (1980 – May 1999), CINHL (1982 – March 1999), and Cochrane Controlled Trials Register were undertaken.

MEDLINE search strategies for optimal sensitivity in identifying randomized clinical trials as recommended by Cochrane Collaboration were used in conjunction with the following phrases and words
#1 (exp naltrexone) or (nalmefene) or (exp narcotic antagonists) or (opioid antagonist)
#2 (exp alcohols) or (exp ethanol)
#3 #1 and #2

An EMBASE search was undertaken by using the above-mentioned strategies applied for a MEDLINE search.

A CINHL search was undertaken by using the following strategies:
#1 (exp alcohols) or (exp alcohol, ethyl)
#2 (naltrexone) or (exp narcotic antagonists) or (nalmefene) or (opiate antagonist)
#3 #1 and #2

The Cochrane Controlled Trials Register was searched by using the words: (NALTREXONE OR NALMEFENE OR NACROTIC ANTAGONIST OR OPIATE ANTAGONIST) AND (ALCOHOL OR ETHANOL).

Additional searches

Du Pont Pharmaceutical and Ivax Corporation were contacted for information regarding unpublished trials. In addition, references of the articles obtained by any means were searched.

TYPES OF STUDIES

All relevant randomized controlled trials (RCTs) clinical control trials (CCTs) were included. As far as possible, missing information relevant to randomization, blinding, etc. was sought by contacting the study's author.

TYPES OF PARTICIPANTS

The participants were people with alcohol dependence, diagnosed by any set of criteria. However, the information of patients whose clinical

conditions were in concordance with the ICD-10 diagnosis of alcohol dependence with current abstinence was excluded.

TYPES OF INTERVENTIONS

1. NTX with/without other biological or psychosocial treatments,
2. NMF with/without other biological or psychosocial treatments,
3. Other opioid antagonists with/without other biological or psychosocial treatments.

TYPES OF OUTCOME MEASURES

The primary outcomes of interest were:

1. Dichotomous data
1.1 Number of patients who relapse to alcohol dependence (as priori criteria),
1.2 Number of patients who return to drinking (but not meet the priori criteria for alcohol dependence),
1.3 Discontinuation rate,
1.4 Death
2. Continuous data
2.1 Number of abstinent days prior to the recommencement of drinking,
2.2 Percentage or number of drinking days,
2.3 Number of standard drinks of alcohol (as priori criteria),
2.4 Number of episodes of heavy drinking (as priori criteria),
2.5 Craving,
2.6 Amount of alcohol consumed,
2.7 Duration of adherence to treatment,
2.8 Patient satisfaction,
2.9 Functioning,
2.10 Health-related quality of life, and
2.11 Economic outcomes.

All outcomes were reported for the short term (less than 3 months), medium term (3 to 12 months), and long term (over 1 year). If any outcome was assessed more than once in a particular term, only the results of the longest duration in that term were considered