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Review

Emerging pharmacotherapies for alcohol dependence: A systematic review focusing on reduction in consumption☆

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ABSTRACT

Background: European Medicines Agency guidelines recognize two different treatment goals for alcohol dependence: abstinence and reduction in alcohol consumption. All currently approved agents are indicated for abstinence. This systematic review aimed to identify drugs in development for alcohol dependence treatment and to establish, based upon trial design, if any are seeking market authorization for reduction in consumption.
Methods: We searched PubMed and Embase (December 2001–November 2011) to identify agents in development for alcohol dependence treatment. Additional studies were identified by searching ClinicalTrials.gov and the R&D Insight and Clinical Trials Insight databases. Studies in which the primary focus was treatment of comorbidity, or $n \leq 20$, were excluded. Studies were then classified as 'abstinence' if they: described a detoxification/alcohol withdrawal period; enrolled patients who had undergone detoxification previously; or presented relapse/abstinence rates as the primary outcome. Studies in patients actively drinking at baseline were classified as 'reduction in consumption'.
Results: Of 602 abstracts identified, 45 full-text articles were eligible. Five monotherapies were in development for alcohol dependence treatment: topiramate, fluvoxamine, aripiprazole, flupenthixol and nalmefene. Nalmefene was the only agent whose sponsor was clearly seeking definitive approval for reduction in consumption. Development status was unclear for topiramate, fluvoxamine, aripiprazole and flupenthixol. Fifteen agents were examined in published exploratory investigator-initiated trials; the majority focused on abstinence. Ongoing (unpublished) trials tended to focus on reduction in consumption.
Conclusions: While published studies generally focused on abstinence, ongoing trials focused on reduction in consumption, suggesting a change in emphasis in the approach to treating alcohol dependence.

Contents

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1. Introduction

Despite the high prevalence of alcohol dependence (Department of Health, 2004; World Health Organization, 2004) and the high burden it poses to society (Rehm et al., 2009; World Health Organization, 2004, 2007), effective management remains a challenge for several reasons. Firstly, alcohol dependence is under-recognized and undertreated. A trial assessing the use of health services for mental disorders in Europe reported that only 8% of patients with alcohol abuse/dependence attend treatment (Alonso et al., 2004). Similar values were reported in the USA; data from a telephone survey and medical record assessment showed that only 10.5% of participants received the recommended care for alcohol dependence (McGlynn et al., 2003). In a review of community-based epidemiology studies, alcohol abuse/dependence had the highest median untreated rate (78%) of the eight psychiatric disorders examined (Kohn et al., 2004). Reasons for these poor treatment rates may include the stigmatization of being labeled an alcoholic and individuals' resistance to stop drinking when treatment programs have traditionally focused on abstinence. Often patients enter treatment under duress from employers or family members (DiClemente et al., 1999; Parhar et al., 2008) and, when treatment is initiated, patient readiness to stop drinking is relatively low, with most patients being ambivalent (DiClemente et al., 1999). Furthermore, both clinicians and patients have little faith in the success of abstinence-focused treatment programs, meaning that clinicians may be reluctant to refer patients with alcohol dependence (Department of Health, 2004). The timing of treatment for alcohol dependence represents another challenge to effective management. Prompt intervention is essential; alcohol use disorder has been shown to have a poor outcome when treatment is delayed (Moos and Moos, 2006).

The existing landscape of pharmacological treatments for alcohol dependence is limited. At present, oral naltrexone (approved in the USA and Europe), injectable naltrexone (USA), oral acamprosate (USA and Europe), disulfiram (USA and Europe) and sodium oxybate (the sodium salt of gamma-hydroxybutyric acid; marketed in Italy and Austria) are indicated for treatment of alcohol dependence. Off-label use is common; for example, in France, there has been a large increase in the off-label use of baclofen for the treatment of alcohol dependence. As originally proposed by Ameisen (2005), proponents of baclofen claim that the drug facilitates low-risk drinking and there has been substantial pressure from patient associations for the acceptance of this off-label use for reduction in alcohol consumption (Rolland et al., 2012). Other agents that are widely used off label in this setting include ondansetron and topiramate (Collins et al., 2006).

All of the agents currently approved for alcohol dependence have market authorization for achieving and maintaining complete abstinence from alcohol. None are indicated for reduction of alcohol consumption, although some are used in this setting. For instance, naltrexone has been investigated for delaying first "heavy drinking day" (HDD) as opposed to "first drink" (Garbutt et al., 1999; Rosner et al., 2008, 2010), and for preventing relapse to heavy drinking (Rosner et al., 2008). These studies suggested that the major benefits of naltrexone are in reducing relapse to heavy drinking and thus number of HDDs, and to a lesser extent increase in abstinence, even in studies where the psychotherapeutic focus was on abstinence (Anton et al., 2006; Volpicelli et al., 1992).

There is, therefore, a need for agents aimed at reducing alcohol consumption. Such agents would be suitable for individuals who would otherwise be deterred from abstinence-based treatment strategies (Ambrogne, 2002). Drugs facilitating a reduction in alcohol use for patients who are not ready to stop drinking altogether would change the attitudes of patients and general practitioners (GPs) to alcohol problems. In the USA, 42% of patients who needed treatment for alcohol problems reported that they had not sought treatment because they were not ready to stop alcohol intake (Substance Abuse and Mental Health Services Administration, 2009); the availability of drugs for reducing alcohol consumption would make it much easier for patients to request help to reduce their alcohol use (Marlatt and Witkiewitz, 2002) and, similarly, it would be much easier for GPs to have available an effective tool to help their heavy drinking patients without having to insist on abstinence. What is more, alcohol use reduction in alcohol-dependent patients might be an intermediary aim to prepare individuals for complete abstinence or a long-term controlled drinking goal (Hodgins et al., 1997). In addition, reduction in alcohol use has been associated with a reduction in alcohol-related morbidity and mortality (reviewed in (Gastfriend et al., 2007)). The reduction in consumption treatment strategy can be used at an early stage of alcohol dependence in primary care and at later stages in specialist care. The validity of the reduction in consumption approach is recognized in the European Medicines Agency (EMA) guidelines on the development of products for alcohol dependence; these guidelines recognize two different treatment goals in alcohol dependence: full abstinence and harm reduction, i.e., reduction in alcohol consumption (EMA, 2010).

The aim of this systematic review was to (a) research the scientific literature, trial registries and proprietary databases to identify drugs in development for the treatment of alcohol dependence and (b) to identify how many, if any, are seeking to establish a specific indication for the reduction in alcohol consumption, by examining the design of the studies identified in the literature search.

2. Methods

2.1. Published literature search strategy

Published abstracts examining pharmacotherapy for the treatment of alcohol dependence were identified by searching PubMed and Embase using the following MeSH terms: "Alcoholism/drug therapy"[Majr] AND ("humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms]). In the hierarchy of MeSH terms, alcoholism captures the desired area of interest, excluding conditions such as acute alcohol intoxication, alcohol withdrawal syndrome, and alcohol-induced physical and mental disorders. Results were limited to the last 10 years (December 2001–November 2011). Additional abstracts were identified by searching the reference lists of full-text articles identified in the literature search.

Abstracts and/or full text-articles were excluded if they were: examining products already marketed for alcohol dependence; conducted in patients with alcohol dependence but the primary focus was treatment of a comorbid disease; conducted in patients with alcohol dependence plus drug dependence; reviews, case studies, letters and commentaries; pilot studies with ≤20 patients in total; conducted in adolescents; focusing on alcohol withdrawal (AW) syndrome (including