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Narrative literature review

Experimental pharmacotherapy approaches to prevention of alcohol dependency

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Summary:

Review of the experimental pharmacotherapy approaches available to reduce craving for alcohol, alcohol consumption, and/or relapse drinking as it pertains to alcohol dependency.

Highlights:

1. Alcohol dependency is a major public health concern in Australia with no single treatment intervention being universally effective.
2. New pharmacotherapies aim to target different features of alcohol dependency, including craving, heavy drinking days and relapse, with some success in recent studies.

3. Nalmefene should be seriously considered for approval in Australia as a treatment for alcohol dependency.

Keywords: alcoholism, baclofen, nalmefene, oxytocin, CERC-501

Word Count: 2833

Experimental pharmacotherapy approaches to prevention of alcohol dependency

Abstract

Background: Alcohol dependency is a major public health concern in Australia. One aspect of the medical management of alcohol dependence is the use of medication to reduce craving for alcohol, alcohol consumption, and/or relapse drinking. However, there exists no single pharmacotherapy that is universally effective amongst patients suffering from alcohol dependency. Thus, personalised approaches to medication and the development of new medication or new uses of established medication may all be necessary to develop effective treatments.

Objective: To review the literature for any potentially effective experimental pharmacotherapy approaches to the prevention of alcohol dependency.

Methods: Using 'MeSH' terms for ‘alcoholism’ and ‘drug therapy’, a literature search on Medline Ovid and PubMed was conducted for preclinical or clinical studies of the effectiveness of any medication in the reduction of alcohol craving, alcohol consumption, and/or relapse drinking. Relevant preclinical and clinical studies since 2013 were retained. Current approved medications such as disulfiram, acamprosate, and naltrexone were excluded from the review.

Results: 14 studies were included for review. Review of the studies identified four drugs as potential pharmacotherapies for the prevention of relapse in alcohol dependence: baclofen, nalmefene, oxytocin, and CERC-501. Findings showed that the efficacy of baclofen in maintaining abstinence from alcohol has not been demonstrated, although there is some evidence for its effectiveness in reducing cravings for alcohol. Nevertheless, clinically significant evidence was found in support of nalmefene and oxytocin’s abilities to reduce alcohol consumption in heavy drinkers. Preliminary studies on CERC-501 have found a decrease in stress-induced relapse drinking in people with alcohol dependency who were previously in remission.

Conclusion: This review found evidence of the efficacy of baclofen, nalmefene, oxytocin, and CERC-501 in the prevention of alcohol dependency, targeting the reduction of alcohol craving, consumption, and relapse drinking. Further investigations using preclinical and clinical trials, including randomised controlled trials, are warranted.

Introduction

Alcohol dependence (AD), also called alcohol use disorder, is a chronic relapsing disorder that is defined by the DSM-5 as the compulsive use of alcohol despite its adverse effects. It may manifest physiologically and/or behaviourally with characteristic symptoms of tolerance, withdrawal, and craving [1-5]. One in five Australians drink at levels that exceed the lifetime risk guidelines, which is more than two standard drinks per day, in turn placing them at risk of AD [6]. AD is a serious problem as excessive drinking can result in serious consequences such as alcoholic cirrhosis, chronic pancreatitis, and Wernicke-Korsakoff syndrome.

The neurobiological mechanism associated with AD is believed to be the chemical stimulation of the mesolimbic dopamine pathway in the reward centre of the brain, the nucleus accumbens. Thus, the mesolimbic dopamine pathway is a major therapeutic target for drugs involved in the treatment of AD [2,5,7]. The medical management of AD serves as a form of tertiary prevention which aims to reduce the severity, discomfort, and disability of the disorder [8,9]. Current approved treatments in Australia, as outlined in the Therapeutic Guidelines (eTG), include disulfiram, acamprosate, and naltrexone. However, these drugs have their own adverse effects [10].

Disulfiram irreversibly inhibits aldehyde dehydrogenase which in turn blocks acetaldehyde breakdown. As a result, a person will experience unpleasant symptoms, such as flushing, sweating, nausea, and vomiting, if alcohol is consumed. These unpleasant symptoms can potentially cause serious adverse effects including dyspnoea, seizures, and arrhythmias [10,11].

Acamprosate derives its therapeutic nature from its ability to decrease the neuronal hyperexcitability experienced with alcohol use and, in turn, prolonging abstinence. This is achieved by modulating the glutamate system. Its major adverse effects include rashes, diarrhoea, and changes in libido [10,12,13].

Naltrexone reduces the pleasurable effects of alcohol by blocking endogenous opioid release. Headache, dizziness, and fatigue are common adverse effects of naltrexone administration. It is contraindicated in patients suffering from acute hepatitis and liver failure as it is metabolised by the liver [10,13,14].

Despite the efficacy of the existing pharmacotherapies, the influence of genetic and environmental factors on a patient's phenotype renders it unlikely that a single treatment intervention will be effective for all individuals who suffer from AD. Hence, experimental pharmacotherapy approaches for the prevention of AD has become of interest in recent literature [5,15].

The focus of the review is on experimental pharmacological approaches that have made recent developmental advancements since 2013 both preclinically and clinically. Pre-existing treatments, such as disulfiram, acamprosate or naltrexone, were not deemed 'experimental' and, thus, were excluded from the review [10].

The aim was to assess the efficacy of experimental medications in reducing relapse drinking, craving for alcohol, and/or alcohol consumption, in turn determining their capability as a tertiary prevention strategy to improve the quality of life of patients with AD.

Methods

A broad literature search strategy on Medline Ovid and PubMed for studies published since 2013 was developed based on focused 'MeSH' terms for ‘alcoholism’ and ‘drug therapy’. The year 2013 was identified as the beginning of the preclinical and clinical studies for the most recent experimental pharmacotherapies for AD. Experimental pharmacotherapies for AD were identified and the literature pertaining to these drugs was considered for possible inclusion in the review. A narrative review approach was chosen because of the diversity of study designs existing in the literature. For the current review, the most salient findings limited to post-2013 studies were extracted.

Results

The following drugs were identified as being the most recent experimental pharmacotherapy approaches to prevention of AD and, hence, were given priority in the review:

1. Baclofen
2. Nalmefene
3. Oxytocin
4. CERC-501

From 3598 citations, 174 citations of potential relevance were retained and subjected to secondary searches to identify evidence relevant to the topic reviewed. After the screening of abstracts and full-text assessment for eligibility, 14 articles remained for inclusion in the review. Of the 14 articles, eight randomised controlled trials (RCT), three prospective cohort studies, two experimental studies and one clinical pilot study were found. Figure 1 presents the PRISMA flow diagram.

We present the results of the four drugs. A summary of the included studies in Table 1.

Baclofen

Baclofen is a GABA B receptor agonist [16-18]. Since GABA B receptors are located in the same areas as the mesolimbic dopamine neurons involved in alcohol addiction, baclofen has become an attractive potential drug for the prevention of AD [16-19]. Nevertheless, the efficacy of baclofen remains controversial in the current literature with inconsistent results between studies [16,17,19,20]. Moreover, the eTG does not currently recommend baclofen for the management of AD. The eTG has requested further research prior to any reconsideration of its role [10].

Of the five studies that were reviewed, four of which were phase II RCT, the varied dosages, low number of patients and durations of treatment and follow-up between studies may explain the inconsistent findings [16-20].

In a 12-week randomised, double-blind, placebo-controlled study of 56 patients, Muller *et al*. [16] demonstrated promising results with more patients treated with baclofen (270 mg/day) maintaining alcohol abstinence in contrast to those receiving placebo (15/22, 68.2 % vs. 5/21, 23.8 %; p=0.014) [16]. However, Ponizovsky *et al*. [20] and Reynaud *et al*.

[17] found no evidence for the superiority of baclofen over placebo in maintaining abstinence from alcohol [17,20]. Reynaud *et al.* conducted an RCT on 320 patients over 20 weeks. The percentage of patients who maintained abstinence in Reynaud *et al.*'s study was low (baclofen (180 mg/day): 11.9 %; placebo: 10.5 %) and not statistically significant between the two groups (OR 1.20; [95 % CI: 0.58 to 2.50]; p=0.618) [18].

There exist a number of important differences between Muller *et al,* Ponizovsky *et al* and Reynaud *et al.*'s studies. Muller *et al.* administered a much higher dosage of baclofen (270 mg/day) [16] compared to Reynaud *et al.* (up to 180 mg/day). Reynaud *et al.* elected to administer baclofen at a lower dose for safety reasons as high dose baclofen may result in severe exacerbations of its adverse effects (fatigue, drowsiness, and dizziness) leading to the inability for patients to tolerate treatment [17]. The large study group size in Reynaud *et al.*'s RCT compared to Muller *et al.*'s strengthens the reliability of Reynaud *et al.*'s statistically insignificant finding (p=0.618) of the effectiveness of baclofen in maintaining abstinence compared to placebo [16,17].

Although Muller *et al.* achieved significant results with a higher dose of baclofen, Beraha *et al*. [19] found no significant difference between low-dose baclofen (30mg/day), high-dose baclofen (270mg/day), and placebo in maintaining abstinence [19]. These divergent results may be explained by the absence of extensive psychosocial treatment in Muller *et al.'*s study which resulted in higher relapse rates in the placebo group (70 %) [16] compared to Beraha *et al.* (25 %) [19]. All patients in Beraha *et al*'s study received psychosocial interventions that consisted of support counselling based on cognitive behaviour therapy principles that aimed to address problems contributing to or resulting from AD [19]. This finding is supported by the high placebo response observed in Ponizovsky *et al.'*s study which also incorporated similar psychosocial interventions to all test groups [20]. Psychosocial intervention might help to reduce AD, thus reducing the effectiveness of baclofen in treatment of AD. Although psychosocial interventions could be effective in reducing AD, patients who lack access or the motivation for intensive psychotherapy might benefit most with baclofen management [19].

Baclofen may play a pivotal role in the prevention of AD as anti-craving drug therapy. Ponizovsky *et al.* and Reynaud *et al.* found a significant decrease in alcohol craving associated with baclofen use in the secondary outcomes [17,20]. This was similarly made evident in the prospective cohort study conducted by Imbert *et al.* [18]. The exact mechanism of baclofen's effect on anti-craving is not fully understood and why baclofen's anti-craving characteristic does not contribute to the maintenance of alcohol abstinence remains in question.

The trials were conducted in various countries and in different settings. Reynaud *et al.*'s RCT was conducted in specialised hospital centres in France [17]. Muller *et al.*'s study was carried out in an outpatient unit in Berlin [16]. Ponizovsky *et al.*'s trial similarly took place in an outpatient unit in Israel [20].

Nalmefene

Nalmefene is the first drug approved in Europe for reduction of alcohol consumption, as opposed to the maintenance of abstinence [21,22]. It is yet to be available in the United States [23] and is not recommended by the eTG in Australia [10]. For many patients suffering from AD, complete abstinence from alcohol is not deemed an achievable aim of tertiary prevention. Thus, nalmefene has the potential to revolutionise current AD management strategies [21,22]. Nalmefene is structurally similar to the widely used naltrexone in that it is an opioid receptor antagonist. Nalmefene, however, has a longer duration of action, higher bioavailability, and no dose-dependent hepatotoxicity [21-23].

Six studies had been conducted to evaluate the effectiveness of nalmefene which included four RCTs and two prospective studies. The first phase III RCT conducted by Mann *et al.* [24] in 2013 demonstrated a significant benefit of using nalmefene in reducing the number of heavy drinking days (HDD) (-2.3 days/month [95 % CI: -3.8 to -0.8]; p=0.0021) [24]. Subsequent studies by Gual *et al.* [25], van den Brink *et al.* [26] and Aubin *et al.* [21] found similar results [21,25,26]. Additionally, van den Brink *et al.* and Aubin *et al.* observed reduced γ-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase elevations with nalmefene administration, thus supporting the hypothesis that nalmefene is

less hepatotoxic than naltrexone and is not contraindicated in patients with acute hepatitis or liver disease [21,26].

Following the positive outcomes of phase III clinical trials, research has since progressed to phase IV open-label studies. Phase IV trials aim to evaluate the effectiveness of nalmefene in a primary care setting. Primary care services play a pivotal role in the management of AD and contrast with the specialist settings where prior phase III trials were conducted. Castera *et al.* [22] and Barrio *et al.* [27] found nalmefene to be efficacious in decreasing HDD and a highly achievable management option in the primary care setting [22,27]. Castera studied 43 primary care sites across four countries (n=378). They found that patients in all countries showed a significant decrease in the number of HDD; the adjusted mean change in the number of HDDs at week 12 compared to the screening visit was -13.1 days/month; [95 % CI: -14.4 to -11.9]; $p<0.0001$ [22]. The present studies raise the possibility that nalmefene could be used as a form of secondary prevention – to reduce alcohol consumption in people with heavy drinking prior to slipping into dependence. It should be noted that, because nalmefene is the only drug available for the reduction of heavy drinking in the treatment of AD, comparisons were made by necessity with drugs indicated for abstinence maintenance in the included studies [21,22,24-27].

Oxytocin

There is growing interest in the use of oxytocin (OXT) as a novel therapeutic target for the prevention of AD following positive results in cocaine, heroin, and methamphetamine addiction [28,29]. OXT is a nanopeptide that, along with its role in prosocial and sexual behaviours, is associated with addiction. It exerts its effects through the dopamine mesolimbic pathway. An emerging body of preclinical and clinical data has suggested that OXT may have a role in reducing alcohol consumption, with the possibility of becoming an alternative to nalmefene intervention. However, the underlying mechanisms remain unknown [29].

One clinical pilot study [28] and one experimental study [29] were found. After studying male Wistar rats under the influence of ethanol, Peters *et al.* [29] concluded that the OXT-

induced blockade of ethanol-induced dopamine release within the nucleus accumbens is responsible for the reduction of alcohol self-administration [29]. Hansson *et al*. [28] develops on Peters *et al.*'s findings from their analysis of the OXT system in alcohol-dependent rats as well as post-mortem brains of humans who suffered from AD and controls. A pronounced upregulation of OXT receptors was discovered in brain tissues of alcohol-dependent rats and deceased patients with AD in response to reduced OXT expression in hypothalamic nuclei. An impaired OXT system, therefore, may explain the effectiveness of OXT administration in attenuating voluntary alcohol consumption [28].

Of particular note in Peters *et al.*'s experiment is OXT's ability to antagonise dopamine release in both ethanol naïve and chronically ethanol-treated rats. As a result, OXT may not be limited to the management and treatment of alcoholism. Similar to nalmefene, OXT has the potential to be utilised as a secondary prevention strategy whereby patients reduce their alcohol intake and thus avoid AD [28].

CERC-501

A new drug therapy for AD that has completed its first preclinical trial in 2018 is CERC-501 (previously LY2456302). CERC-501 is an orally available kappa opioid receptor (KOR) antagonist. Accumulating evidence has revealed the crucial role KOR's play in the stress reactivity and negative emotionality associated with alcoholism rendering CERC-501 a potential clinical candidate. The experimental study on male Wistar rat models by Domi *et al.* [30] concluded that CERC-501 is effective in blocking stress-induced, however not cue-induced, relapse drinking. This proves to be the opposite of the widely used mu opioid receptor antagonist naltrexone. Naltrexone selectively inhibits cue-induced alcohol relapse. Therefore, CERC-501 may be more beneficial in patients with stress-driven alcohol use making it a potentially positive addition to the existing AD drug therapies [30].

Discussion

There exists no single treatment intervention that is universally effective amongst all patients suffering from AD. Thus, personalised approaches to medication, and the development of new medication or new uses of established medication, is necessary to

develop effective treatments [5,15]. The present review aimed to review and summarise the current literature on the efficacy of baclofen, nalmefene, OXT, and CERC-501 as novel pharmacotherapies for the prevention of AD.

The review found some evidence-based results that support the further research and inclusion of experimental pharmacotherapies for AD. Firstly, the five studies examining the effect of baclofen over placebo on the maintenance of abstinence had mixed results, with one study showing a trend that favoured baclofen [16] and four studies showing no difference [17-20]. However, three of the five studies found evidence to support the use of baclofen as an anti-craving therapy [17,18,20]. Additionally, hypotheses exist surrounding the use of baclofen as a replacement for psychosocial intervention in patients who lack the access or motivation [19]. Baclofen's efficacy as a mainstream pharmacotherapy for AD is yet to be proven. Further phase II clinical trials evaluating baclofen’s role as an alternative to psychotherapy management in AD and as anti-craving pharmacotherapy is recommended prior to advancement to phase III trials.

Evidence from six studies suggest that nalmefene is an efficacious treatment for the reduction of HDD in patients suffering from AD. These findings are strengthened by the several RCTs that were conducted, the large sample sizes included in the RCTs, and the wide range of countries where the studies took place [21,22, 24-27]. The results support the approval of nalmefene as a treatment for AD in Australia.

OXT may also reduce the number of HDD following the discovery that an impaired OXT system drives alcohol self-administration., although, the number of studies is small (two) and limited to experimental trials on animals [28-29]. Several questions remain unanswered at present. Investigations into the therapeutic dose of OXT in AD, the adverse effects of OXT, and OXT’s sex-specific responses (due to the gender differences that exist in the OXT system) are necessary.

The review found weak evidence to support CERC-501's effectiveness in reducing stress-induced relapse drinking due to the existence of only one experimental study in animals

[30]. Further research is required to establish CERC-501's required dose and its adverse event profile in a human population.

The main observed adverse effects of baclofen and nalmefene remained comparable with the currently approved pharmacotherapies for AD, namely naltrexone. The adverse effects of baclofen include fatigue, drowsiness and dizziness [16,17,19] and those of naltrexone include nausea, dizziness and fatigue [24-26]. However, it is worthwhile noting that Beraha *et al.* observed the highest frequency of adverse effects in the high-dose baclofen group. Whilst it is hypothesised that high-dose baclofen is more therapeutic, particularly in the absence of psychosocial intervention, the increased safety risk associated with high-doses reinforces the prematurity of large-scale prescription of baclofen [19].

The main confound of the review is the addition of psychosocial treatment which most studies do not describe in detail and is capable of affecting medication efficacy. Another major difficulty in comparing studies is the lack of uniformity of drinking outcome measures. In addition, definitions for outcomes such as 'HDD' or 'relapse' vary between studies.

Conclusion

Alcohol dependency is a chronic relapsing disorder that is an important public health concern in Australia. As patients with AD express varying phenotypes, rendering no single intervention universally effective, experimental pharmacotherapy approaches are indicated for secondary and tertiary prevention strategies. Baclofen has not consistently been shown to be effective for the maintenance of alcohol abstinence, however, it may be effective as an anti-craving therapy. Research on nalmefene and OXT has found them to have efficacy in reducing heavy drinking, suggesting promise as new treatment strategies. Despite being early in the research pipeline, CERC-501 has also demonstrated promise as an effective drug for the prevention of stress-induced relapse drinking. The conclusions of this narrative review are limited by the substantial heterogeneity of study designs in the literature. Further research using experimental studies and RCTs is warranted.

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