Pharmacology & Therapeutics 153 (2015) 10–24

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Pharmacotherapy for alcohol dependence: A stratified approach

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ARTICLE INFO

Available online 16 May 2015

Keywords:
Alcohol dependence
Pharmacogenetics
Typologies
Stratified medicine

ABSTRACT

Alcohol dependence is a common disorder in many societies worldwide, and remains difficult to identify and treat. It is also a risk factor for many secondary non-communicable diseases. Pharmacotherapy is one available treatment option, but appears to be underutilised in practice. Major barriers to use of medications in this area include lack of clinical guidance and questionable efficacy. However, for each medication there appears to be a subpopulation that responds positively, and understanding the moderating factors to treatment efficacy is an important research goal. Thus, this review provides a narrative regarding potential stratification techniques in pharmacological treatment of alcohol dependence, with a specific focus on typologies and pharmacogenetics. In addition, we discuss the basic background of stratified medicine and recent studies on genetic predisposition to alcohol dependence.

A growing repository of data exists for both approved and non-approved pharmacotherapies, but failure to replicate findings, inadequate sample sizes, and insufficient funding has resulted in a translational gap. Implementing evidence-based stratified/personalised therapy and identifying new therapeutic agents may lead to improved clinical outcomes and reduced financial burden. Despite some promising findings to date, much work is still required.

Contents

Abbreviations: 5HT, 5-hydroxytryptamine; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ASN, asparagine; ASP, aspartate; DBH, dopamine beta-hydroxylase; EOA, early onset alcohol dependence; HTR7, 5-hydroxytrytamine receptor 7; GABA, γ-aminobutyric acid; LOA, late onset alcohol dependence; NMDA, N-methyl-D-aspartate; OPRM1, opioid receptor mu-1; OPRD1, opioid receptor delta-1; OPRK1, opioid receptor kappa-1; SLC6A4, solute carrier family 6 member 4.

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http://dx.doi.org/10.1016/j.pharmthera.2015.05.010
0163-7258/

1. Introduction

Alcohol dependence is a major global public health concern, with the use and abuse of alcohol considered a leading risk factor for many non-communicable diseases (Jones et al., 2008). The mortality rate is high in this population, being nearly four times the age-adjusted rate for people without alcohol dependence (NICE, 2009). There are further social and economic costs linked to excessive alcohol drinking, with the annual global bill estimated at 760 billion Euros (Rehm et al., 2009). The aetiology of alcohol dependence is heterogeneous, and manifests from complex interactions between the environment and genes. This heterogeneity has been postulated as a confounder to treatment utilisation and efficacy, especially for pharmacotherapy (Litten et al., 2012). Empirical evidence is emerging however which suggests that a "stratified" approach to treatment may help optimise outcomes. Understanding the moderators that influence positive (or adverse) responses to a specific medication in a subgroup, or more desirably an individual, will assist healthcare practitioners in making more informed decisions when prescribing, and hopefully result in improved clinical outcomes.

This review aims to provide a narrative of recent advances in the pharmacological treatment of alcohol dependence. There will be a focus on specific subgroups and underlying factors that may influence the efficacy of each medication, thus providing a rationale for a stratified approach to treatment. Specifically, attention will be given to stratification by typology and advances in pharmacogenetics. This review will start by providing a basic overview of stratified medicine. The main section of the article will cover the three medications approved for alcohol dependence treatment by The Medicines and Healthcare Products Regulatory Agency (UK) and Food and Drug Administration (USA): naltrexone, acamprosate and disulfiram. We will then discuss more contemporary drugs, including nalmefene, which was recently approved by The European Medicines Agency. This review will not cover the use of drugs during withdrawal from alcohol (detoxification); reviews on this topic are available elsewhere (for example, Amato et al., 2010; Amato et al., 2011; Minozzi et al., 2010). Furthermore, we do not cover the utility of psychological interventions either when used alone or in combination with pharmacotherapy. We acknowledge that this might be viewed as a limitation but we are unable to consider this variable in the scope of this review. Indeed, it is possible that more personalised approaches on the type and intensity of psychological intervention may also be of use in these patients.

2. Stratified approach to treating alcohol dependence

2.1. What is stratified medicine?

Current medical practice is largely empirical, with treatment based on a "trial and error" paradigm targeting large patient populations. Although this can be effective, many drugs have a significant number of non-responders or cause adverse reactions. Stratified medicine aims to identify these groups via shared biological or risk characteristics, and tailor subsequent treatment accordingly. One example of stratified medicine in practice is the improved efficacy of trastuzumab for the treatment of metastatic breast cancer in patients who overexpress the human epidermal growth factor-2 (*HER2*) gene (Slamon et al., 2001). Personalised medicine and precision medicine are related terms often used inter-changeably in this area to describe treatment at individual patient-level rather than subgroup clustering. It has been suggested that personalised medicine is an additional step on the patient therapeutic continuum (Trusheim et al., 2007).

2.2. Clinical stratification in alcohol dependence

Identifying moderators/predictors of treatment efficacy is an important goal for any therapeutic aid. Those that are pertinent to alcohol dependence are presented in Table 1.

Table 1
Common variables used in the stratification of alcohol dependence.

Variable	Comment
Gender	The majority of research in this field is conducted in males. Alcohol dependence is more prevalent in males but alcohol generally affects females more severely.
Age	The majority of alcohol abusers are in their teens or twenties, with the highest prevalence of those undertaking treatment for AD being in their forties. The majority of sample populations have mean ages in their forties.
Ethnicity	The availability of alcohol varies depending on societal, cultural and religious views. The majority of research has been conducted in those of European descent. Non-Caucasian populations are underrepresented in alcohol research, making universal application of results difficult. A subgroup of East Asians experience an adverse reaction to alcohol associated with a mutation in *ALDH2* which has been hypothesised to be protective against alcohol misuse.
Family history	Alcohol dependence has a substantial hereditary component, 40–60%. However, a consensus is yet to be reached on the optimal description of positive family in this area of research. This lack of uniformity and the small number of studies negatively impacts on the overall strength of the evidence.
Typology	In typology research, attempts are made to group individuals depending on the characteristics of their alcohol dependence, with the aim to guide diagnosis, predict prognosis and provide targeted treatments. The typologies discussed within this review are presented in Table 3 (for a dedicated review see Leggio et al., 2009).
Co-morbidities	Excessive alcohol consumption is a risk factor for ~60 diseases/conditions. Also, those with alcohol use disorders can have underlying mental-health disorders that are caused by or are responsible for their alcohol misuse. Individuals with comorbidities are often excluded from research for reasons relating to safety, inherent complexity and maintaining sample homogeneity. The majority of medications utilised in alcohol dependence are metabolised in liver which is often compromised with excessive alcohol consumption (e.g., alcoholic liver disease). Baclofen has received some interest an alternative treatment for alcohol dependence as it is predominantly excreted by the kidneys.
Genetics	Please see pharmacogenetics sections and Table 2.

2.3. Pharmacogenetics

Pharmacogenetics is the study of genetic variation in drug response, with the aim of maximising clinical effectiveness and minimising toxicity by selecting the right drug for the right patient at the right dose. Such work is vital to ensure more precise prescribing which will benefit the patient and reduce costs. Rapid advances in sequencing technology coupled with international projects (e.g. International HapMap Project and Human Genome Project) have produced a wealth of data and repositories in this field. Several areas of medicine have already been influenced by pharmacogenetics, for example warfarin dosing (Pirmohamed et al., 2013), predicting responders to interferon-α in hepatitis C (Pirmohamed, 2011) and identification of individuals at risk of abacavir hypersensitivity reaction (Martin et al., 2012).

The use of pharmacogenetics in drug treatment for alcohol dependence is in its infancy relative to the above examples. The most advanced empirical evidence exists for the mu-opioid receptor gene (*OPRM1*) polymorphism, Asn40Asp (rs1799971), which has been reported to predict naltrexone response (Chamorro et al., 2012). Pharmacogenetic studies relating to the treatment of alcohol dependence are summarised in Table 2 and discussed in the relevant sections of this review.

2.4. Genetic predisposition to alcohol dependence

Results from family studies indicate substantial heritability for alcohol dependence, approximately 40–60% (Kendler et al., 1992; Kendler et al., 1997; Milne et al., 2009; Prescott & Kendler, 1999). Despite advances in genetic testing and related analytical methods over the last two decades, the genes and associated variants responsible for this