

## CHALLENGES TO MEDICATIONS DEVELOPMENT IN TREATING ALCOHOL DEPENDENCE: AN INTERNATIONAL PERSPECTIVE

SUMMARY OF A SYMPOSIUM HELD AT THE ESBRA CONGRESS, PRAGUE, 13 SEPTEMBER 2003

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(Received 27 February 2004; first review notified 3 March 2004; in revised form 23 March 2004; accepted 28 March 2004)

**Abstract** — Few medications for treating alcohol dependence exist. Greater partnership is needed between academia and the pharmaceutical industry to develop, licence and market efficacious medications for treating alcohol dependence. Methodologies that span the divide between preclinical and large-scale clinical studies need to be developed in order to provide sufficient information on safety, toleration, drug-interaction profile and efficacy, with which to guide development decisions. Due to the heterogeneous nature of alcohol dependence, the effort of developing an efficacious medication is likely to be enhanced by clearer choices about the characteristics of the population. Careful consideration of potential mechanism of action of the putative therapeutic medication should enable the appropriate choice of drinking endpoint. The pharmaceutical industry in collaboration with academia might need to develop new approaches to determining appropriate treatment endpoints with regulatory bodies. The investment risk to industry should be appraised not only in terms of the rather poor results of previous marketing efforts but with a view to the opportunity to penetrate a potentially enormous and largely untapped market.

### INTRODUCTION

The purpose of the symposium was to identify reasons for the apparent poor record of introduction of new medications for treating alcohol dependence over the last 50 years. During this time, only disulfiram, naltrexone and acamprosate have achieved any kind of regulatory approval and clinical use. A major challenge recognized at the outset is that medications development is normally the province of the pharmaceutical industry, rather than of academic research, but there are several reasons why the industry has been unenthusiastic about developing medications in this area. To progress, we must try to increase the commitment of industry to this area and/or we must seek greater academic involvement in the research and development process. In either case, the general aim must be to reduce the current level of risk for development of medications in this field. At present, there are several uncertainties that limit enthusiasm for this endeavour, including the following. (1) Investment risk: what will the financial or medical return be on the amount of expenditure? (2) Regulatory risk: what do the Food and Drug

Administration (FDA) and the European Union (EU) authorities require prior to approval, and will this change? (3) Marketing risk: how much investment will be required to develop a relatively new market in very heterogeneous clinical specialties? (4) Health liability risk: will a novel medication interact unpredictably with alcohol or with alcohol-related disease once it reaches general use? The symposium was designed to identify challenges at all levels of funding and investigation, and to make recommendations as to ways to improve the situation.

### FUNDING OF MEDICATIONS DEVELOPMENT

The first topic of discussion related to the funding of medications development against the background of funding of alcohol research in general. In the US, the major source of funding is through the National Institute on Alcohol Abuse and Alcoholism (NIAAA), which specifically supports a medications development programme. This has now been made a top priority for the coming years; indeed, the National Institutes of Health (NIH) has made improved treatment for alcoholism one of its 10 primary research goals. However, it is recognized that there are specific challenges for NIH-based funding for medications development programmes, particularly when these require applied research and development in academic institutions. These include the high costs, intellectual property implications and peer-review evaluation of applied research. NIAAA is considering several

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The views expressed in this paper do not necessarily represent those of National Institute on Alcohol Abuse and Alcoholism (NIAAA).

measures to increase effectiveness of medications development in this area. These include bringing together preclinical and clinical research, and making partnerships within government and between academic and industry researchers, to provide a more integrated approach to the problem. The major challenge in the US is how to use funds most effectively for medications development. In particular, the problem is how to achieve a medications development approach in those laboratories best equipped to study alcohol dependence and alcohol-related organ damage. In Europe (and indeed the rest of the world), funding levels for alcohol research are much lower and there are no specific programmes for medications development. The major sources of funding are the EU and national governments, but the alcoholic beverage industry, research charities and pharmaceutical industry also contribute. Indeed, industry-supported research on medications development may be greater in Europe, perhaps because the 'medical model' for treatment is more accepted in Europe than it is in the US. However, the major challenge in Europe seems to be to improve overall levels of funding for alcohol research and then to allocate a significant proportion to medications development. In general terms, recent evidence of the cost-effectiveness of treatment of alcohol dependence with naltrexone and acamprosate might be an effective means of lobbying government to allocate more funds to research on new medications.

#### PRECLINICAL RESEARCH AND DEVELOPMENT

At the level of preclinical research, the pharmaceutical industry seems unclear about the therapeutic and molecular targets that might be important in alcohol dependence. Improved medications are needed, particularly for treating relapse into alcohol use and for alcohol-related organ damage, and many potential molecular targets for drugs that may either prevent relapse into alcohol use or reduce organ damage have been identified. Most of the research responsible for these advances currently takes place in academic, university-based laboratories, but this rarely goes much further in terms of developing usable medications. With regard to relapse, the limited clinical success of naltrexone and acamprosate strongly suggests that opioid receptors and glutamate receptors might be valuable molecular targets. It is clearly necessary to identify which of these has the most impact on clinical outcome but, from a preclinical perspective, 'high throughput' pharmacological screens are already available to identify compounds with actions at these targets and research directed toward these is common in the pharmaceutical industry. However, for any of the novel active compounds discovered to be considered as potential medications for alcohol dependence, there needs to be a screening hierarchy that will identify those compounds that should reach the next phase of investigation. Thus potentially valuable compounds should progress through a sequence of cellular screens, simple whole-animal screens and more complex animal models, that will predict a reasonable likelihood of success in the clinic.

For alcohol dependence, this type of hierarchy of screens and models does not yet exist. In particular, there is a major

gap between (1) identification of compounds with appropriate molecular actions and (2) their testing in complex animal models of relapse and reinstatement. A relatively simple rat paradigm, the 'alcohol deprivation effect', may prove valuable as an intermediate screen for anti-relapse action. Indeed, this simple and reliable model of 'relapse self-administration of alcohol' is already being used as a screen in some programmes. Such screens are not high throughput but if they can be shown to be of good predictive validity for clinical use, they will be invaluable for medications development. Future research might focus on developing screens that have a more rapid throughput while retaining predictive validity. These might not be identical for each molecular target, for example potential medications based on glutamate receptor antagonism might be screened by reduction of the alcohol withdrawal syndrome, whereas efficacy of opioid receptor antagonists might be related to ability to reduce alcohol-induced place preference. Validation of these tests in terms of their predictive validity and reproducibility as simple screens is an essential step in the process of their acceptance. For organ damage, there are some simple cell-based screens that might be useful for medications development but these have not generally been evaluated for predictive validity, even in animal models. If the pharmaceutical industry is to become involved in this research or, indeed, if preclinical research and development is to be performed in academic laboratories, there is a need to fill the 'high throughput screening gap' in medications development in this field. This will require considerable discussion between academic researchers and industry scientists so as to apply the medications development techniques from industry to the potential molecular targets derived from basic research. A forum to agree on appropriate screens and to exchange information on research and development techniques seems essential if novel medications are to be developed specifically for their potential use in alcohol dependence.

#### TRANSLATIONAL RESEARCH IN ALCOHOL DEPENDENCE

The field of medications development for alcohol dependence needs to find methodologies that span the gaps between preclinical and clinical research and between human experimentation and clinical trials (Johnson and Ait-Daoud, 2000). In this way, throughput of medications for treating alcohol dependence would be increased. There are two ways to view the research required. The usual approach is *a priori* research in which drugs are screened (as above) for their effects on alcohol drinking and/or relapse in animal models, with the assumption that this will be predictive either of efficacy in humans or for identification of potential molecular targets. Ideally, the preclinical studies can then be translated directly into clinical studies. Small-scale clinical studies might be used to bridge the gap between preclinical and clinical research, thereby providing preliminary information on safety and efficacy prior to the conduct of large multi-centre trials. While small-scale clinical studies are prone to producing either false-positive or false-negative conclusions with respect to efficacy, some agreed translational

approach would provide information on safety, toleration and dosing strategies that could guide companies in their decision-making process.

In order to achieve this, there is now a need for *a posteriori* research in which drugs that do have some clinical efficacy are evaluated in human experiments to establish both their psychopharmacological mechanisms and the predictive validity of these paradigms (as for animal models, see above). The *a posteriori* approach may be difficult to fund by the peer review process because, at first sight, it seems to repeat studies on drugs of proven clinical efficacy at a lower level of complexity. However, for medications development to progress there needs to be both feed-back and feed-forward interactions between all levels of research. Clinical trials are much too costly and too problematic (see below) to be the only way of evaluating all potential medications. In particular, simple human tests with analogous animal models would be extremely valuable for translational drug development if they could be shown to predict clinical efficacy. Once again, these animal models and human tests may not be identical for all types of agent. For example, naltrexone-like drugs might be evaluated based on their inhibition of positively reinforcing effects of alcohol, whereas acamprosate-like drugs might require analysis of effects on subjective withdrawal-like symptoms. Reproducible tests of these types in animals and humans could be extremely valuable. As a simple example, human clinical experiments on a novel agent might identify the range of plasma concentrations likely to prove efficacious in clinical trials. Currently this is largely guesswork. For this type of translational research to succeed, there needs to be an increase in communication between ‘animal’ and ‘human’ researchers, and between these groups and treatment providers.

#### CLINICAL TRIALS AND THE REGULATORY AUTHORITIES

Once potential medications have been identified at the preclinical level, the problems become even more difficult and more expensive. Not only is it necessary to establish clinical efficacy, it is necessary to do this in a way that is acceptable to the regulatory authorities in different countries. In contrast to many other areas of medications development, there are no agreed international guidelines from the regulatory authorities for the conduct of clinical trials in alcohol dependence. There is consequently variation between conduct of trials in different centres and between countries. Clinical trials in Europe also tend to be more ‘naturalistic’ and more prolonged than are trials in the US, making it difficult to compare data across continents. Identified areas in which guidelines would be particularly valuable include minimizing the bias associated with patients leaving trials prematurely and a preferred main end-point to assess outcomes. However, it must be recognized that the preferred main end-point probably cannot be identical for all medications because of the need to match clinical end-point with the mechanism of action of the drug. For example, although anti-relapse drugs such as naltrexone and acamprosate might share an end-point such as ‘cumulative abstinent days’ during the trial, this would not be appropriate for an agent aimed at reducing excessive drinking without

necessarily producing abstinence at all. Such an agent might be therapeutically very valuable but would not be identified as effective by a purely ‘abstinence-based’ outcome measure. Overall, it is clear that pre-trial motivation for patients to reduce their alcohol consumption must be assessed and incorporated into study design and/or statistical analysis. Also, ideally, outcome measures should reflect clinical relevance, quality of life and economic cost–benefit analysis. Regardless of the complexity, it would certainly increase industry enthusiasm for development of medications if some guidelines for acceptability were issued by the appropriate regulatory authorities. These guidelines should recognize that pharmaceutical industry-sponsored studies may not be capable of addressing long-term outcomes, quality-of-life issues and the rarer consequences of heavy drinking. Nevertheless, despite the difficulties in assessing trials, some existing drugs have effect sizes for prevention of relapse that compare favourably with the efficacy of other established psychopharmacological medications, for example the effect sizes of antidepressants against depressive illness or, perhaps more relevant, anti-smoking compounds versus tobacco use.

#### IMPROVING CLINICAL EFFICACY

There are several approaches by which the modest effect sizes currently observed might be improved. Thus, because alcohol dependence is a multi-factorial condition, effect sizes might be dramatically improved if clinical subtypes could be matched to specific treatment mechanisms (or if medications could be used in combination, see below). However, there is little agreement between clinicians on which subtype classification to use and many of those available have been developed for purposes other than prediction of treatment outcome. A major challenge to the development of improved treatments is to identify a consensus on subtyping alcohol dependence in a way that is designed specifically with pharmacotherapeutic response in mind. This problem might be solved in another way if it were possible to choose therapy based on identification of genetic subtypes of the specific molecular targets for drugs. For example, genetic differences in the mu opiate receptor might predict naltrexone efficacy. Another approach to hitting the appropriate therapeutic target in a population of dissimilar patients is to use a combination of dissimilar pharmacological treatments. For example, the limited evidence to date suggests that combinations of naltrexone and acamprosate may be more effective than either drug alone. The results of a large-scale clinical trial in the US, the COMBINE study (COMBINE Study Research Group, 2003), will soon be available to address this possibility in a more definitive manner. Another potential explanation for the success of combinations of treatments is that these may target different mechanisms for relapse that occur together in some patients. Regardless of the precise reasons, it seems very likely that combinations of treatments will increase efficacy and this is an important step in the development of new medications and in the use of existing medications. A major challenge will be the manufacture and marketing of combined treatments, particularly when these are produced by different pharmaceutical companies.

### INCREASING CURRENT USE OF APPROVED MEDICATIONS

Although naltrexone and/or acamprosate are available for use in many countries worldwide, the number of patients receiving these pharmacological treatments is extremely disappointing (Mark *et al.*, 2003). In contrast to the 'best clinical practice' (which is probably to use these medications together with validated psychosocial treatments), the majority of patients in therapy seem to be receiving treatments that either have never been assessed or have actually been discredited in the past. Similarly, the use of approved pharmacological agents for treatment of alcohol dependence is very low when compared with that of antidepressants and antipsychotic drugs. Because alcohol dependence has greater disease prevalence in the population, at least when compared with psychosis, and as evidence-based reviews of approved medications for alcohol dependence [for example, of acamprosate and naltrexone in Sweden (Swedish Health Technology Board, 2001; Brooks, 2002) and in Scotland (Health Technology Board of Scotland, 2002)] confirm their efficacy, these low rates of use are difficult to explain. We appear to be doing a poor job of disseminating persuasive information on the benefits of existing treatments. Unless this can be improved, any development of new and improved medications will be largely futile. From the industry perspective, aggressive marketing of such medications is vital to ensure both that physicians prescribe, and that their patients take, these effective drugs. Unfortunately, this did not occur to a sufficient extent for naltrexone to penetrate the market effectively either in Europe or in the US. In this regard, NIAAA has funded two studies on the barriers to more widespread naltrexone use. In addition to the refusal of patients to take the medication, high cost, small effect size and side-effects, these barriers include lack of organizational support in promoting the use of naltrexone. Even the best new medications have to overcome conservatism and suspicion before becoming widely used and there are additional challenges for medications aimed at alcohol dependence (see below). Without a proper marketing and support system, no medication will penetrate this new and difficult market effectively, and without effective market penetration there will be little economic or medical value.

### IMPROVING THE SOCIETAL CLIMATE FOR MEDICATIONS DEVELOPMENT

A major factor in the low level of clinical use of validated pharmacotherapy may be the general societal view that alcohol dependence is a 'behaviour disorder' rather than a 'medical condition'. It could be argued that this is similar to the societal view of depression and psychosis before pharmacotherapy transformed outcomes of these conditions. This viewpoint is compounded by the important current role of psychosocial treatment in alcohol dependence and by the role of the social services in recovery and rehabilitation. This has led to some antipathy toward medical treatment of alcohol dependence by the psychosocial treatment community, who may feel that their position will be undermined by effective pharmacotherapy. Unless these barriers are overcome,

medications that are effective treatments will never reach some patients who need them and might never be profitable. This alone might dissuade the pharmaceutical industry, or any other researcher interested in the practical value of his/her research, from becoming committed to medications development for alcohol dependence; this is perhaps the major challenge to an effective strategy. Better dissemination of information and more aggressive 'educational marketing', particularly to primary healthcare practitioners and including non-medical personnel, is required if medications development is to have a brighter future. This is not only the responsibility of those pharmaceutical companies with effective medications; government and professional organizations must also play an active role. Specifically, there is a compelling need to explain and integrate medical and psychosocial treatments so that they are accepted by physicians and patients alike. The aim must be to reduce opposition to the introduction of pharmacotherapy and the best approach may be to convince healthcare practitioners that great potential value resides in augmenting the efficacy of both kinds of treatment by delivering them together.

### CONCLUSIONS

Two themes emerged from the talks and discussion in the symposium. First, in treating alcohol dependence, 'one size does *not* fit all'. Thus, from basic science through translational research, clinical trials and clinical use, alcohol dependence is multi-factorial and may require much more than a single type of medication for treatment. Despite this we must attempt to reach broad agreement on how we seek, evaluate and use medications in the future. Radically different expert viewpoints will be perceived as uncertainty and will reinforce industry (and clinical practitioner) suspicion of this area. Second, medications development is a continuum — divisions between basic and clinical science and between academia and industry are artificial, arbitrary and counterproductive. If we are to progress, we need to do so on several fronts and we need to communicate each other's views and concerns continuously. In this regard, this symposium was valuable as a forum for exchange of ideas and perspectives between basic and clinical researchers and between academia and industry. It should be regarded as the first step in leading to a better climate for medications development in our area. For this to occur, not only must we identify some of the major challenges, as has been done above, but we must also take steps to meet them and to reduce the barriers that currently exist. This will undoubtedly be more difficult and will require many incremental steps. Industry enthusiasm for this area will not be generated overnight, and neither will academic laboratories immediately become philosophically and technically capable of industry-like approaches to medications development. However, we must capitalize on the relative success of naltrexone and acamprosate as medications and build on this.

Unless we act now, the impetus will be lost; we hope that this symposium and review will be the first of many dedicated to this subject. For more information and for an opportunity to contribute your own views, please visit the web site of the International Society for Biomedical Research on Alcoholism (ISBRA).

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