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The Alcohol Clinical Trials Initiative (ACTIVE): Purpose and Goals for Assessing Important and Salient Issues for Medications Development in Alcohol Use Disorders

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Although progress has been made in the treatment of alcohol use disorders, more effective treatments are needed. In the last 15 years, several medications have been approved for use in alcohol dependence but have only limited effectiveness and clinical acceptance. While academics have developed some 'standards' for the performance of clinical trials for alcohol dependence, they vary considerably, in the type of populations to be studied, the length of trials, salient outcome measures, and data analyses to be used (especially in the treatment of missing data). This variability impedes the commercial development of medications to treat alcohol dependence. Using a model similar to that used to develop an expert consensus for medications to improve cognitive aspects of schizophrenia (MATRICS) and in the treatment of pain (IMMPACT), a workgroup has been formed under the auspices of ACNP, known as the ACTIVE (Alcohol Clinical Trials Initiative) group, to evaluate data from completed clinical trials to develop a consensus on key issues in the conduct of clinical trials in alcohol dependence. ACTIVE consists of academic experts, industry representatives, and staff from the Food and Drug Administration, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse. This paper describes the rationale behind the effort, its history and organization, and initial key questions that have been identified as the primary focus of the workgroup. Future papers will focus on knowledge gained from the re-analysis of completed trials and provide consensus opinions regarding the performance of clinical trials that might be undertaken in the future.
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RATIONALE AND HISTORY OF THE ACTIVE PROCESS

Alcohol use disorders affect large numbers of individuals throughout the world. In the United States, during a 1-year period, 7–9% of adults have an alcohol use disorder and many more are heavy or 'at risk' drinkers (Substance Abuse and Mental Health Services Administration (SAMHSA), 2004; Hasin *et al*, 2007). The costs of excessive drinking are estimated to exceed $200 billion a year (Rehm *et al*, 2009), much of which is accounted for by health-care expenditures. Despite the health, social, and economic burden of excessive drinking, most individuals with alcohol problems go unrecognized and do not seek treatment (Hasin *et al*, 2007). Reasons for this include the lack of affordable and science-based treatment resources, as well as a lack of appreciation and education of both the public and treatment professionals in the evidenced-based treatment of addiction. Although greater availability of medications to treat alcohol dependence could alleviate this resource deficiency, pharmaceutical companies have been reluctant to expand their drug development portfolio into this area. They perceive a lack of a clear clinical trial methodology as increasing the cost burden of what they consider a 'risky' drug-development commitment. This perception, built on much informal discussion between companies and alcohol

Some of this information has been presented in part at the ACNP meeting in Miami Beach, Florida in December 2011.

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clinical trial experts, as well as the growing need for regulatory authorities (including the Food and Drug Administration (FDA) in the United States and the European Medicines Agency) to provide the industry with informed guidance, led to an effort to define the questions to be addressed and an effective process by which to address them.

In May 2007, a meeting sponsored by the American College of Neuropsychopharmacology (ACNP) was convened to discuss 'Opportunities and Impediments for Medications Development for Alcoholism and Other Substance Abuse.' Clinical trial experts from 9 universities and representatives of 29 pharmaceutical companies or industry affiliates, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the FDA attended the meeting. There was a consensus that all stakeholders needed to work together to address the opportunities and impediments to the process that exist (Table 1).

At that meeting, information was collected on areas of interest and concerns regarding 'opportunities to develop medications to treat addictive disorders'. The initial goal was to develop an overall strategy and determine the next steps to be taken. A substantial proportion of industry participants either 'agreed or strongly agreed' that there was a 'substantial market' for medications to treat nicotine and alcohol dependence, but a smaller market for medications to treat cocaine and opioid dependence.

All three groups of attendees agreed that the neuroscience knowledge, including known biological targets for treatment, together with the substantial market for alcohol dependence medications warranted further drug development in this area. However, there was not a consensus on the clarity of regulatory requirements: only 28% of industry representatives thought that regulatory issues were clear compared with 70% of academic and government agency officials. There was a similar lack of consensus on which are the optimal, or most appropriate, clinical trial methods, with 53% of industry representatives, 88% of academics and 67% of government personnel of the opinion that methods for clinical trials in alcohol dependence were clear. In sum, all groups agreed that regulatory issues and clinical trials methodology needed clarification.

There was a consensus that the next step should be to constitute an ongoing workgroup to address these issues. After much discussion, assessment of feasibility, and potential avenues of support, the Alcohol Clinical Trials Initiative (ACTIVE) workgroup was formed to focus on concerns regarding the development of medications for alcohol use disorders.

The ACTIVE workgroup is modeled after the IMMPACT project (Turk *et al*, 2003) on pain medications and the MATRICS project (Buchanan *et al*, 2005) on cognitive enhancing drugs for schizophrenia. Five (eventually this number increased to seven) pharmaceutical companies support the project, with continued ACNP infrastructure support. Companies send up to two representatives each, to join nine ACNP member/affiliate academic experts and five government-affiliated experts (two from the FDA and two from NIAAA) along with a representative from NIDA (who could use this effort as a template for medication development for clinical trial initiatives to treat drug abuse). Subsequently, a representative of the European Medicines Agency (EMA) was asked to join the ACTIVE workgroup with the expressed hope of calibrating, or harmonizing, approaches taken in the United States and Europe.

The ACTIVE workgroup plans to address the issues that were deemed most important (see below) by analyzing salient clinical trial data and through presentations/consultation from outside experts, thereby leading to discussion and consensus building among the participating members. The next two sections will articulate issues that are of importance to industry and provide a history of the specific medications that are currently approved to treat alcohol use disorders. These sections highlight the salient issues in medications development as a starting point for future analyses.

CHALLENGES AND OPPORTUNITIES IN MEDICATION DEVELOPMENT FOR ALCOHOL USE DISORDERS: AN INDUSTRY PERSPECTIVE

Developing pharmacological treatments for alcoholism is challenging. Alcoholism is certainly not a unitary disorder

Table 1 Opportunities for Interaction Among Key Groups in the Development of Medications to Treat Alcohol Use Disorders

	Academic	NIAAA/NIDA	FDA
NIAAA/NIDA	NIAAA/NIDA funds individual early discovery trials and coordinates collaborative discovery and comparative medication trials.		
FDA	Academics sit on FDA review panels and provide consultation regarding medication approvals.	NIAAA/NIDA assists FDA in establishing guidelines for study design, duration, and outcome measures.	
Pharmaceutical companies	Companies seek consultation from academics on appropriate indications for medication use, population selection, study design, and data analysis. Companies can provide academics and NIAAA/NIDA with novel compounds in development or approved medications for clinical trials.	NIAAA/NIDA can help industry to identify experienced investigators and provide advice on study design and outcome measures.	Companies discover new compounds for clinical development. FDA provides guidance to Companies on clinical study design, outcome measures, and analyses. FDA reviews New Drug Applications for marketing approval.

and reliable phenotypic and biological indicators have not yet been identified to subtype the condition to permit more specific pharmacological interventions. For this and other reasons, the efficacy of currently approved therapies is not generally considered robust. The primary care physician, the health-care provider most likely to identify a person with excessive alcohol use and thus have the greatest opportunity to intervene, is often unfamiliar with pharmacological options (Mark *et al*, 2009). Thus, these practitioners must not only become comfortable with the risk, benefit, and magnitude of the clinical effect expected, but must also be willing to raise the issue of treating a problem that the patient may be resistant to acknowledge even exists. Finally, the use of medications is often not embraced by traditional treatment approaches (eg, Alcoholics Anonymous).

These issues increase the risk that any new discovery/development effort will ultimately fail, and reduce the likelihood that a company would consider launching a new development program. Thus, it is even more important that current stakeholders in improved alcohol treatment, including industry, academia, and relevant government agencies, all establish a clear and rational consensus for key development issues, including reliable targets and end-points to assess a meaningful treatment success. Such a consensus should also include input from primary care physicians, the treatment community, and patients. Although pharmaceutical and biotechnology companies seek to develop treatments that are medically important, commercial success is also required. Initial commercial success not only justifies the continued marketing of a specific product but also encourages more companies to seek better and more novel therapies. For this reason, the successful translation and use of products to treat alcoholism must eventually include better education of both health-care providers (Mark *et al*, 2009) and the general public regarding the availability and appropriate prescription of these medications. Primary health-care providers should also be educated on the advantages of using clinical/medical laboratories to identify individuals at greatest risk for alcohol use disorders (Fleming and Mundt, 2004; Miller and Anton, 2004). In time, the alcohol research community—having identified organ-based cardiovascular, metabolic, psychiatric, and mortality advantages associated with the cessation or reduction in alcohol use—may begin to apply them to the assessment of medication efficacy, thereby helping to address a significant public health problem. One such example might be a reduction in blood pressure secondary to reduced drinking and abstinence (Stewart *et al*, 2008). A medically relevant outcome such as this could fuel interest in the pharmacological treatment of alcohol dependence.

Despite this longer-term promise, a collective effort must first establish which outcome measures are most appropriate for clinical trials and how to define the successful treatment of alcohol use disorders. Otherwise, the perceived obstacles to developing new therapies will likely be seen by industry as far greater than the opportunities, even as increased awareness of alcoholism grows and scientific advances further elucidate mechanisms and potential targets.

A BRIEF HISTORY OF MEDICATIONS APPROVED BY THE US FDA FOR THE TREATMENT OF ALCOHOL DEPENDENCE

The focus of this brief review is on the four drug products approved by the FDA in the United States for the treatment of alcohol dependence. (Although other medications are approved for specific use in treating acute alcohol withdrawal symptoms, that indication is outside the scope of this brief review.) The applications for three of these products were supported by efficacy data from clinical trials reviewed by the FDA. The basic design of the trials and analytic approaches to the data that supported marketing approval are described below and summarized in Table 2. The fourth drug, disulfiram, was approved in 1951, before the statutory requirement that drugs be demonstrated to be effective before marketing. The 1969 determination that disulfiram was effective was made during the Drug Efficacy Study Implementation process, based on literature review

Table 2 Design of Studies Supporting Regulatory Approvals of Alcoholism Treatment Medications in the United States

	Sample size	Duration	Endpoint analyzed	Completion rate
Oral naltrexone #1	41/Arm	12 Weeks	Various, including % subjects abstinent, % subjects with no 'heavy drinking days'	P: 51% A: 58%
Oral naltrexone #2	52/Arm	12 Weeks	Various, including % subjects abstinent, % subjects with no 'heavy drinking days'	P: 60% A: 71%
Acamprosate #1	~60/Arm	90 Days	% Subjects abstinent	P: 52% A: 69%
Acamprosate #2	~180/Arm	360 Days	% Subjects abstinent	P: 35% A: 48%
Acamprosate #3	136/Arm	48 Weeks	% Subjects abstinent	P: 40% A: 58%
Depot naltrexone	~200/Arm (total) ~17/arm (no lead-in drinking)	6 Months	% Subjects with no 'heavy drinking days'	Overall sample P: 64% A: 64%

Abbreviations: A, active medication; P, placebo. All studies were randomized, double-blind, placebo-controlled, parallel-group design.

by a panel convened by the National Academy of Sciences/National Research Council. A larger emphasis in this overview has been placed on Vivitrol, a long-acting injectable form of naltrexone, since it was the most recent approval and therefore best reflects the current FDA approach to this area of drug development.

The 1994 approval of oral naltrexone tablets, marketed as ReVia, for the treatment of alcohol dependence, was based on two investigator-initiated studies. The FDA did not review either protocol prospectively, and one specific primary endpoint was not required. The study population in both trials consisted of alcohol-dependent patients who were abstinent at study entry. In one of the studies, a minimum of 10 days of abstinence was emphasized in the review. A variety of analyses were considered, including the proportion of subjects maintaining abstinence and the proportion completing the study without relapse to heavy drinking over the 12-week observation period. Both studies are described in the published medical literature (Volpicelli *et al*, 1992; O'Malley *et al*, 1992) but it should be noted that the FDA analyzed the raw data and had access to some additional data not included in the published reports.

The application for acamprosate, marketed as Campral, approved in 2004, was supported by three pivotal trials, one lasting 3 months and two lasting roughly a year each. In addition, safety data and summaries of efficacy results were provided for six additional 6-month studies and three 1-year studies. All of these studies were designed and completed outside of the United States before the initial interactions occurred between the commercial sponsor and the FDA; therefore, the FDA did not provide input on study design or analysis. A single 6-month study in the United States was also conducted; this study did not demonstrate a significant advantage for acamprosate over placebo.

The protocols for two of the pivotal studies did not clearly specify a primary analysis, and various analyses were performed. The third pre-specified a survival analysis. The sponsor proposed that an analysis of the mean number of cumulative days of abstinence be considered the primary endpoint. However, the method of ascertainment of the number of drinking days was not sufficiently systematic to allow for precise counting of the number of days drinking or not drinking. The common endpoint applied (retrospectively) to all three studies was the percentage of patients remaining continuously abstinent throughout treatment, because this seemed to be credibly determined and represented a clear clinical benefit. In the three European pivotal efficacy studies, subjects randomized to acamprosate were more likely than subjects randomized to placebo to be assessed by the clinician as having been abstinent http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-431_Campral.cfm.

The 2006 approval of depot (long-acting injectable) naltrexone, marketed as Vivitrol, was based on efficacy data from a single study, using a regulatory pathway that permitted the application to rest, in part, on the FDA's previous finding of efficacy for oral naltrexone (ie, 505(b)(2) submission). The previous Agency finding of efficacy for oral naltrexone was based, as noted above, on two studies in recently detoxified alcohol-dependent subjects abstinent at study entry. Notably, the labeling for oral naltrexone does not describe this feature of the studies or stipulate that patients should be abstinent at treatment initiation. The single study submitted in support of efficacy was a 6-month placebo-controlled study in alcohol-dependent outpatients who were not required to refrain from drinking between screening and study drug initiation, although some did. In designing the study, the sponsor had discussed with the FDA the possibility of defining patterns of drinking behavior short of complete abstinence as treatment success. Although it has also been noted that the consumption of limited quantities of alcohol may actually confer a health benefit in patients without alcohol use problems, conventional wisdom has long held that sustained, controlled drinking at low levels has not seemed feasible for the alcohol-dependent patient. However, to explore the possibility that this feature of alcoholism may be amenable to treatment (perhaps pharmacologic treatment in particular), this study was designed to evaluate the event rate of heavy drinking. A heavy drinking event was defined as a day in which a male patient consumed at least five standard drinks and a female patient consumed at least four standard drinks (one standard drink is equivalent to 12 oz of 5% beer, 5 oz of 12–17% wine, 3 oz of fortified wine, or 1.5 oz of 80 proof liquor). The event rate was to be calculated over the duration of treatment (ie, over 24 weeks or up to the time of treatment discontinuation). A number of secondary analyses of drinking patterns were also pre-specified, including analyses of the proportion of patients who were treatment responders (responder analyses) as requested by the FDA.

The protocol specified an analysis that aggregated the drinking data by treatment group rather than evaluating the percentage of patients in each treatment group who were considered 'treatment responders'. However, the development program for this product took place when outcome measures for alcoholism treatment trials were in evolution. During the course of development, the Agency became aware of information developed by NIAAA that provided empirical support for the selection of a responder definition based on drinking patterns. The FDA's understanding of the information was that individuals who drank occasionally, but never heavily, during the observation or survey period, were at very low risk of experiencing the adverse social and occupational consequences of alcohol use, even if those individuals had a history of alcohol problems. Therefore, a pattern of drinking that included 'no heavy drinking days' could be considered a 'non-risky' drinking pattern, even in alcohol-dependent patients. The FDA believed that the proportion of patients achieving and maintaining complete abstinence from alcohol drinking remained an endpoint of indisputable significance, but noted that the evidence suggested that the proportion of patients able to maintain a non-risky drinking pattern would be of similar significance. Although an analysis based on alcohol consumption provides only indirect evidence of treatment benefit (true clinical benefit would need to capture the impact of treatment on how patients actually feel and function, and improved psychosocial, occupational, or physical well-being is often not measured and is unlikely to be captured in a 6-month study), this responder definition (ie, no heavy drinking days over the study period) appeared to be an appropriate surrogate for clinical benefit. Therefore, FDA review of the application gave greater attention to the analyses that were originally designated as secondary.

As a result of the lack of prior information about the effect of naltrexone in subjects drinking at baseline, FDA reviewers also examined (using both responder analyses and event rate analysis) the effect of depot naltrexone on the subgroups of patients who were abstinent before treatment initiation, compared with the patients who were drinking.

Only 9% of study participants did not drink alcohol during the 7-day lead-in period before treatment initiation. In this subgroup, the applicant's analysis showed that treatment with depot naltrexone was associated with a very substantial reduction in the event rate of heavy drinking. Even with fewer than 20 subjects per group, statistical significance was reached in this subgroup. In contrast, only a nonsignificant reduction in heavy drinking, using the applicant's analysis, was seen in the 91% of patients who consumed alcohol in the week before treatment initiation.

The FDA's approach to the responder analysis demonstrated a similar phenomenon. For the responder analysis, patients who did not drink heavily from the end of the 'grace period' to the end of the treatment period were operationally defined as responders. FDA allowed for a grace period in the analysis, during which patients who sampled alcohol would not be counted as treatment nonresponders for two reasons: to allow for engagement in treatment, and to address the hypothesis that naltrexone works by reducing the reward experienced when alcoholics consume alcohol, thus decreasing the potential for a 'lapse' to turn into a 'relapse.' In the FDA's analysis, in the study population as a whole, few subjects achieved a complete absence of any heavy drinking days, and no effect of naltrexone treatment was apparent when the rates were inspected. In contrast, the success of the very small subgroup who were abstinent at baseline was impressive and a clear treatment effect was observed http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021897_toc_Vivitrol.cfm.

Therefore, the study drug seemed to be effective only in the small subgroup who did not drink during the lead-in period. Taking into consideration the lack of any prior evidence that naltrexone has an effect on drinking in patients who are drinking at treatment initiation, the FDA determined that efficacy had been demonstrated only in the subgroup of patients who have been able to refrain from drinking for at least a brief period (several days) at the time of treatment initiation.

Going forward, the FDA generally views alcoholism as a chronic disorder and alcoholism treatment drugs as maintenance treatments. The current approach of chronically administered drugs for chronic conditions, in general, is that the default observation period is 12 weeks (after any grace period, titration, and so on). However, if there is a reason that the effect cannot be observed in that time period, the studies should be longer. For example, obesity studies are 1 year in duration http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf. The FDA has been asking for 6-month studies for alcoholism treatment because there are data indicating that drinking patterns over 3 months may not be stable or representative of future experience (Zweben and Cisler, 2003). It is also reported that periods of abstinence are quite common among alcohol-dependent individuals: periods of abstinence lasting at least 3 months were reported by 62.3% of a heterogeneous group of alcohol-dependent individuals (many not treatment seeking) through retrospective/historical interviews (Schuckit *et al*, 1997).

KEY QUESTIONS IN ALCOHOL DEPENDENCE CLINICAL TRIAL DESIGN AND ANALYSIS

At the first ACTIVE workgroup meeting, attendees rated the most important issues to be addressed in the development of medications for alcohol dependence. A questionnaire (available at http://www.acnp.org/programs/taskforce.aspx) containing 26 items in six domains: study population, study duration, data collected, analysis, study response-rates, and general issues were completed by participants. The top seven concerns rated on a scale of 1 (most important) to 3 (least important) are shown in Table 3.

Question 1: How Should Missing Data Be Handled?

A daily-calendar method to measure alcohol consumption (Sobell *et al*, 1988, 1996) has become the standard for the collection of daily drinking data, which can be analyzed over different time intervals. Missing data, which are problematic, are mostly attributable to subjects leaving the study prematurely. Although premature discontinuation may reflect relapse, this cannot be assumed; some people who have been continuously abstinent leave treatment because they think they are 'cured,' while others who are doing well may find a job that interferes with their attendance. So, the imputation of drinking data could be biased. A determination is needed on how best to minimize missing data and what the effect various imputation methods have on medication efficacy results and effect sizes.

Question 2: What is the Most Appropriate Trial Duration?

This is an important issue since it affects costs, patient convenience and motivation, dropout rates, stability of response, and sample size estimates for clinical trials. The goal is to identify an optimal balance of trial length, observed response, and the duration of response. However, it is also important to establish that behavior observed in a brief clinical trial is predictive of longer-term response, if the medication is continued. The goal would be to utilize current clinical trial data sets and other sources of longitudinal data to address these concerns.

Question 3: Can Reduction in Drinking from a Pre-Study Baseline be Considered as a Primary Endpoint in Clinical Trials? If so, What Reduction is Clinically Significant?

Although 'no heavy drinking days,' the endpoint that is currently recommended by the FDA represents a reduction in drinking, since it considers 'success' as both abstinence as well as drinking below a daily level of five drinks or men or four drinks for women, other alternatives (eg, reduction from an individual's pre-treatment drinking level) have also been proposed. As there are currently few data sets that

Table 3 Most Important Questions and Concerns (Out of a Total of 26) Regarding Clinical Trials in Alcohol Dependence as Rated by ACTIVE Workgroup Members

Rank	Question	Average score of respondents*	Addressed with available data?
1	How should missing data be handled as a result of study dropout? Should a data substitution/ imputation method be used to 'fill in' the missing values?	1.1	Yes
2	Is there data to show that a longer period of observation is needed to document a stable response, or that a shorter period will give sufficient information to predict longer-term results?	1.3	Yes
3	What is a 'clinically significant' change from pre-randomization drinking if 'reduction' in drinking might be considered as a primary endpoint in clinical trials?	1.4	Maybe
4	What is the effect of selecting subjects who are drinking daily up until day of randomization versus those that are abstinent for some days before randomization on drinking outcome endpoints?	1.5	Yes
5	What are the advantages and disadvantages of including subjects with psychiatric co-morbidities in clinical trials?	1.5	No
6	If self-reported abstinence is contradicted by biological markers (including breath analysis), should the subject still be rated as being abstinent? Should composite measures of drinking and biomarkers be used in clinical trials?	1.5	Yes
7	Should dimensional scales of alcohol severity, consequences, and quality of life be obtained in clinical trials? Can significant change in severity, alcohol consequences, or QOL be a satisfactory end-point?	1.5	Maybe

Rated on a scale of 1 (most important) to 3 (least important).
Full questionnaire available at http://www.acnp.org/programs/taskforce.aspx

provide the information needed to determine how reduced drinking, short of complete abstinence, is related to alcohol-related symptoms, functioning and long-term outcomes, this question is difficult to answer. The benefits of reduced drinking have, therefore, been difficult to quantify. Nevertheless, some well-designed clinical trials have enrolled actively drinking individuals whose goal was either reduced drinking or, ultimately, abstinence (Johnson *et al*, 2007). As achievement of these goals translated into improvement in alcohol-related consequences (Johnson *et al*, 2008), re-analysis of this data set could shed light on this issue.

Question 4: What is the Effect of Selecting Actively Drinking Individuals *vs* Those that have had Some Abstinence Before Randomization?

This question is independent of the specific outcome measure to be used. It addresses the issue of what effect abstinence or current drinking at trial entry has on such things as placebo response, treatment effect size, drop-out, and so on? The answer might depend on the expected pharmacological action of the medication under study. For instance, a drug that promotes abstinence by normalizing sleep and reducing irritability or the urge to drink associated with alcohol withdrawal might only be effective in subjects who begin treatment while abstinent. In contrast, drugs that block reinforcement might work equally well, or better, if a person is actively drinking. Other factors, such as a subject's motivation for abstinence, the rate of study retention, medication interactions with alcohol, post-randomization alcohol withdrawal symptoms might also influence this decision.

Question 5: What is the Effect of Including Subjects with Both Alcohol Dependence and Co-Morbid Psychiatric Disorders?

Despite high rates of co-morbidity of alcohol dependence and other psychiatric disorders (Hasin *et al*, 2007; Kendler *et al*, 1993), alcohol treatment trials have generally excluded individuals with co-occurring disorders. The reasons for this practice are to avoid variation in subjects' drinking motives (eg, stress reduction *vs* self-medication of non-specific symptoms such as sleep disturbances, anxiety, and mania), which could interact with a medication's specific mode of action. Such variation could reduce the medication's effect size because of greater variation in treatment response. However, it is possible that these issues are exaggerated or unfounded. The evaluation of this issue will be limited by the relative paucity of multisite trials of co-morbid alcoholics using medications known to be effective in alcoholics without co-occurring disorders.

Question 6: Should Biomarkers and Consequences of Drinking be Included as Endpoints and, if so, Should They be Used Independently or Concomitant with Self-Reported Drinking?

Self-reported drinking data have limited validity. Although, in placebo-controlled trials the error variance because of invalid reporting of drinking behavior should be equally distributed among the groups, this remains a concern because it can limit the effect size and generalizability of the clinical trial results. Thus, are there adequately sensitive and specific biomarkers (eg, blood or urine tests) of drinking behavior that can be used to supplement verbal reports or to limit the amount and detail of self-report data to be

collected? In addition, while drinking-related health and psychosocial consequences might vary among individuals with different levels of drinking, should the quantification of known drinking consequences be compared with, or combined with, drinking amounts to provide a more global or composite picture of treatment efficacy? These approaches might also contribute to the body of science in this area (Cisler and Zweben, 1999; Zweben and Cisler, 2003; Anton *et al*, 2006).

Question 7: Should Multi-Dimensional Scales (Patient Reported or Investigator Rated) Be Used to Give a Broader Picture of Drinking Consequences and/or Improvement?

Although the FDA has suggested that abstinence, or absence of heavy drinking, are clinically meaningful outcomes that can support product approval, these drinking outcomes are surrogates for the actual treatment benefit, that is, improved functioning in a variety of domains (eg, physical, social, and emotional). It has not been convincingly demonstrated that a clinically relevant benefit accrues to drinking less (short of abstinence or possibly no heavy drinking). Thus, to interpret incremental improvements in drinking, clinical trials must assess improvement in other important domains of functioning. One challenge to this assessment is that the psychosocial and health consequences of drinking generally accumulate over time and their rate of occurrence can vary substantially among individuals. Multidimensional assessments that measure the impact of drinking on salient aspects of functioning have been proposed, including the Alcohol Dependence Scale (Skinner and Horn, 1984) and the Drinker Inventory of Consequences (DrInC) (Miller *et al*, 1995). The limitations of specific multidimensional instruments must be taken into consideration to avoid problems in study design, data analysis, and study interpretation. The FDA provides guidance for the development and use of patient-reported outcome (PRO) instruments to support treatment benefit and drug product claims. Nevertheless, how these should be applied to alcohol dependence trials needs better definition.

The ACTIVE workgroup has a detailed plan to address six of these seven questions with currently available data. To answer these questions, and others related to them, we searched for data sets from alcohol clinical trials amenable to secondary analyses. The following criteria were applied in selecting the appropriate studies: (1) randomized, double-blind, placebo-controlled, multi-site clinical trials of a large number of alcohol-dependent subjects to approximate pivotal study requirements of the FDA; (2) availability of daily drinking data throughout the trial; (3) availability of other relevant measures, such as consequences and biochemical and physiological effects of drinking, and quality of life (QOL); (4) availability of demographic and baseline clinical information of randomized subjects; (5) trial duration of at least 3 months; (6) rates of study attrition not exceeding 40% during the first 3 months of the trial; and (7) accessibility for analysis by ACTIVE investigators.

We identified five alcohol clinical trials: (1) the COMBINE study, a 4-month, 11-site, 9-arm trial evaluating the efficacy of naltrexone and acamprosate in combination with two behavioral therapies in 1383 alcohol-dependent subjects (Anton *et al*, 2006); (2) a multicenter, 14-week, 17-site study comparing topiramate with placebo in combination with a brief intervention in 371 alcohol-dependent subjects (Johnson *et al*, 2007); (3) a 6-month, 24-site pivotal trial that randomly assigned 627 alcohol-dependent adults to receive one of two doses of long-acting naltrexone combined with a low-intensity psychosocial intervention (Garbutt *et al*, 2005); (4) the VA Naltrexone Cooperative Study, a 12-month, 15-site trial in which 627 alcohol-dependent veterans were randomly assigned to receive placebo or daily oral naltrexone for 3 or 12 months in combination with individual counseling (Krystal *et al*, 2001); (5) a 12-week randomized trial comparing aripiprazole with placebo in 295 alcohol-dependent subjects who also received weekly cognitive-behavioral therapy (Anton *et al*, 2008). As new multi-site trials become available, those that meet the selection criteria will be considered for addition to this group.

Using these data sets, the first set of analyses will include: (1) evaluation of various drinking endpoints (both dichotomous and continuous measures) with respect to treatment effect; (2) validation of drinking endpoints against non-drinking outcomes, including consequences of drinking, QOL, drinking biomarkers, and physiological changes; (3) investigation of the effects of varying lengths of 'a grace period'—the period early in the trial preceding the time at which outcomes are first considered in the analysis; (4) determination of the optimal duration for the treatment phase of a clinical trial; (5) comparison of outcomes using imputation or non-imputation of drinking data as a means of handling missing data; and (6) examination of the nonspecific effects on treatment outcome associated with abstinence during the period immediately preceding randomization. Results of these analyses will be presented in subsequent papers that form the basis for the publication of the consensus opinion of the ACTIVE workgroup on key issues in clinical trials of medication for alcohol dependence.

PATIENT-REPORTED OUTCOMES—BEYOND DRINKING REPORTS

PROs are used to determine the clinical impact of alcohol use disorder interventions beyond what is assessed through typical efficacy measures of abstinence or reductions in drinking. We review here what PROs are, what makes an acceptable PRO, how they may be communicated to patients and physicians, and finally briefly describe how the ACTIVE workgroup is collaborating with industry to refine a specific PRO for clinical trials on alcohol dependence.

PROs include any report coming directly from the patient about how he or she functions or feels in relation to a health condition and its treatment. PROs measure symptoms that are known only to the patient and provide the patient's perspective on the risks and benefits that treatment may offer. Assessment includes, but is not limited to, measures of symptoms, function, and QOL. QOL researchers use PROs to provide the relevance of changes in the efficacy measure in terms that reflect the impact on the patient's life. This is especially true for alcohol use disorders, where large

personal and economic consequences of the illness are present. The DrInC—the primary QOL measure used in the assessment of alcohol use disorders—was created in 1995 as a patient-reported measure of drinking-related consequences. The DrInC includes five subscales: physical consequences, intrapersonal consequences, interpersonal consequences, social responsibility, and impulse control related to drinking (Miller *et al*, 1995).

Required documentation to support a health-related quality of life (HRQL) claim includes evidence that all of the important effects of the condition and treatment on HRQL from the patient's perspective are measured. As many constructs measured by PROs (eg, general QOL) may be vague in meaning or may vary in interpretation depending on the population studied, the scientific community has tried to specify the reliability, validity, ability to detect change, and the clinical appropriateness of recent PRO measures. Regulatory agencies including the FDA and EMA have issued guidance for the use of PRO measures for labeling claims of new medications. The FDA final guidance published in December of 2009 (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf) specifies the level of evidence required to identify concepts and the conceptual framework from the patients' view when developing an instrument.

When viewing the DrInC in light of the FDA Guidance, several issues warranted further investigation. The instrument was apparently not developed with extensive patient input, and its conceptual framework and measurement properties were not well documented. In many instances, scientists have modified the DrInC to meet the needs of a particular study. In addition, the DrInC, being 50 items in length, may be too burdensome in some clinical trial or research settings. Currently, PROs have not been included in the package insert of FDA-approved medications for the treatment of alcohol use disorders and therefore are not communicated to patients or physicians. The ACTIVE team is providing consultation on an ongoing, multi-year qualitative and quantitative assessment and revision of the DrInC (initiated by Eli Lilly) to meet requirements for inclusion in drug labels. This evaluation is currently in progress and will be made public when finished.

SUMMARY

More cooperation is needed among academia, government agencies, and the pharmaceutical industry to improve study designs and outcome measures for clinical trials to test medications to treat alcohol use disorders. A critical mass of interested professionals from these various groups has come together to support the ACTIVE workgroup's goals and objectives. Although the number of multisite clinical trials is limited, the ACTIVE process has created a mechanism and infrastructure to provide a consensus opinion on best practices that can be updated as new clinical trial data become available. The ACTIVE workgroup plans to use data from completed trials as a starting point to address the important questions that remain unresolved and that impede clinical trials in the field. Data from future multisite studies will be used to refine and improve the consensus as they become available. This approach is similar to the pain assessment program developed by IMMPACT, where study design, population characteristics, outcome measures, and analytic plans evolved quickly following an initial examination of existing data. (Turk *et al*, 2003).

Substantial elements within government, industry, and academia support the ACTIVE process, which is beginning to achieve its goals. This paper introduces the ACTIVE workgroup to the field, states its goals and work plan, and enumerates the type of questions it intends to examine. Future publications will present data to address some of these questions and will ultimately be incorporated into a consensus publication from the ACTIVE workgroup.

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REFERENCES

Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J (2008). A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol* **28**: 5–12.

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM *et al* (2006). Combine Study Research Group: combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* **295**: 2003–2017.

Buchanan RW, Davis M, Goff D, Green MF, Keefe RS, Leon AC *et al* (2005). A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull* **31**: 5–19.

Cisler RA, Zweben A (1999). Development of a composite measure for assessing alcohol treatment outcome: operationalization and validation. *Alcohol Clin Exp Res* **23**: 263–271.

Fleming M, Mundt M (2004). Carbohydrate-deficient transferrin: validity of a new alcohol biomarker in a sample of patients with diabetes and hypertension. *J Am Board Fam Pract* **17**: 247–255.

Garbutt J, Kranzler H, O'Malley S, Gastfriend D, Pettinati H, Silverman B *et al* (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. *JAMA* **293**: 1617–1625.

Hasin DS, Stinson FS, Ogburn E, Grant BF (2007). Prevalence, correlates, disability, and comorbidity of *DSM-IV* alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* **64**: 830–842.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K *et al* (2008). Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* **168**: 1188–1199.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K *et al* (2007). Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* **298**: 1641–1651.

Kendler KS, Heath AC, Neale MC, Kessler RC, Eaves LJ (1993). Alcoholism and major depression in women. *Arch Gen Psychiatry* **50**: 690–698.

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA (2001). Naltrexone in the treatment of alcohol dependence. *N Engl J Med* **345**: 1734–1739.

Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR (2009). Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend* **99**: 345–349.

Miller PM, Anton R (2004). Biochemical alcohol screening in primary health care. *Addict Behav* **29**: 1427–1437.

Miller WR, Tonigan JS, Longabaugh R (1995). The Drinker Inventory of Consequences (DrInC). An Instrument for Assessing Adverse Consequences of Alcohol Abuse (Test Manual). U. S. Department of Health and Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism: Bethesda, MD. DHHS Pub. No. 95-3911.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992). Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry* **49**: 881–887.

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* **373**: 2223–2233.

Schuckit MA, Tipp JE, Smith TL, Bucholz KK (1997). Periods of abstinence following the onset of alcohol dependence in 1853 men and women. *J Stud Alcohol* **58**: 581–589.

Skinner HA, Horn JL (1984). *Alcohol Dependence Scale: Users Guide*. Addiction Research Foundation: Toronto.

Sobell LC, Brown J, Leo GI, Sobell MB (1996). The reliability of the alcohol timeline follow back when administered by telephone and by computer. *Drug Alcohol Depend* **42**: 49–54.

Sobell LC, Sobell MB, Leo GI, Cancilla A (1988). Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict* **83**: 393–402.

Stewart SH, Latham PK, Miller PM, Randall P, Anton RF (2008). Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. *Addiction* **103**: 1622–1628.

Substance Abuse and Mental Health Services Administration (2004). *Results from the 2003 National Survey on Drug Use and Health: National Findings* SAMHSA 2004 ed. Office of Applied Studies: Rockville, MD, NSDUH Series H-25, DHHS Publication No. SMA 04-3694.

Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB *et al.* (2003). Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* **106**: 337–345.

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992). Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* **49**: 876–880.

Zweben A, Cisler RA (2003). Clinical and methodological utility of a composite outcome measure for alcohol treatment research. *Alcohol Clin Exp Res* **27**: 1680–1685.