Alcoholism: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2015
Clinical/Medical

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of alcoholism.[2] There are many different terms, definitions, and diagnostic criteria that have been used to describe this condition. However, in this guidance, we use the term *alcoholism* to describe patients with alcohol use problems that would make them candidates for treatment with medication. As the World Health Organization (WHO) notes,[3] alcoholism is a "term of long-standing use" and is "generally taken to refer to chronic continual drinking or periodic consumption of alcohol which is characterized by impaired control over drinking, frequent episodes of intoxication, and preoccupation with alcohol and the use of alcohol despite adverse consequences." Further discussion of terminology can be found in Appendix 1.

We are issuing this guidance to better communicate our current thinking on the appropriate endpoints for clinical trials of drugs to treat alcoholism, and to apprise sponsors of possible alternatives to abstinence-based endpoints, which have often been considered an unattainable threshold in the clinical trial setting, and which may be considered a hindrance to clinical development for drugs to treat alcoholism. This guidance provides supporting information for the endpoints as appropriate measures of clinical benefit. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anesthesia, Analgesia, and

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] http://www.who.int/substance_abuse/terminology/who_lexicon/en/ (accessed 2/1/14)

Addiction Products (DAAAP), pharmaceutical sponsors, the academic community, and the public.[4]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[5]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEVELOPMENT PROGRAM

In all diagnostic schemes, alcoholism is identified by behavior — continued self-administration of alcohol despite physical and psychosocial consequences. Alcoholism is understood to be a chronic, relapsing disorder that may require long-term and even lifelong treatment. The aim of treatment is often expressed as an effort to modify drinking behavior, but the actual desired effect is improvement in physical and psychosocial consequences. Therefore, drinking behavior (particularly that snapshot of behavior that can be observed during the brief window of a clinical trial) is considered a surrogate endpoint, not a direct measure of how the patient feels or functions. Trials intended to show direct effects on physical or psychosocial consequences of drug use would need to be long and large, and may be impractical. As such, sponsors do not need to demonstrate a direct effect on the physical and psychosocial consequences of alcoholism in alcoholism clinical trials, but they should show modifications in drinking behavior ascribed to a particular treatment that are likely to translate to improvement in the physical and psychosocial consequences.

Because drinking behavior is considered a surrogate endpoint, sponsors should document a pattern of behavior that can be reasonably predictive of clinical benefit (e.g., improvement in the way the patient feels or functions). Patients who attain and sustain complete abstinence from alcohol may be assumed to accrue clinical benefit. Thus, trials showing a difference in the proportion of patients who attain and sustain complete abstinence may support an indication of treatment of alcoholism. We believe analyses of existing data also support the use of another valid surrogate endpoint defined by a pattern of reduced drinking, described as *no heavy drinking days*. *Heavy drinking days* are defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as days when the patient consumes more than four standard drinks (men)

[4] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs to treat alcoholism.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

or more than three standard drinks (women). Standard drinks are defined in the United States as containing 14 grams of alcohol, such as would be found in a standard *shot* of hard liquor, a 12-ounce bottle of beer, or a 5-ounce glass of wine. An analysis of the proportion of patients who attain and sustain a pattern of drinking that never exceeds the heavy drinking definitions may be appropriate.

We anticipate this pattern to be attained within a reasonable, behaviorally, and pharmacologically justified *grace period*, and that it be sustained for at least 6 months of treatment. We do not necessarily expect that efficacy will be sustained after the drug is withdrawn if the drug is intended to be administered chronically.

DAAAP's current recommendation is for trials of 6 months' duration, with a primary endpoint of the proportion of patients who do not have any heavy drinking days during the observation period (percent no heavy drinking days). Background explanations to support the validity of this endpoint as a surrogate for clinical benefit may be found in Appendix 2.

A. General Considerations

1. Early Phase Clinical Development Considerations

As part of their early phase clinical development program, sponsors should consider drug-alcohol interactions and may need to conduct formal drug-alcohol interaction trials. When designing the early phase clinical development program, sponsors should also be aware of, and give consideration to, the possibility that patients with chronic alcoholism or with hepatic impairment might have different pharmacokinetic/pharmacodynamic profiles from the general population.

2. Drug Development Population

In general, the target population for this indication should be adults who are seeking treatment for alcoholism. Early phase trials in which alcohol is administered generally should be conducted in nontreatment-seeking individuals, although there may be some circumstances under which administration of alcohol to treatment-seeking individuals may be justified.

To fulfill the requirements of the Pediatric Research Equity Act (PREA),[6] studies in adolescents (12 through 16 years old) may be required. Sponsors should assess the size of the treatment-seeking population to determine whether studies in this population may be practicably conducted. A waiver will be considered based on this assessment.

[6] PREA, originally enacted on December 3, 2003 (Public Law 108-155), codified many of the elements of the pediatric rule, and established requirements for studies of certain drugs and biological products used in pediatric patients. PREA (section 505B of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355c), reauthorized by the Food and Drug Administration Amendments Act of 2007, as Title IV, on September 27, 2007 (21 U.S.C. 355c), and made permanent in 2012 with the passage of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), requires pediatric studies for certain drugs and biological products.

3. Efficacy Considerations

Generally, two adequate and well-controlled trials will be needed to support an efficacy claim for this indication.

4. Safety Considerations

The safety database should be sufficiently sized, from both the standpoint of sample size and length of observation, to assess the safety of a drug intended for the treatment of a chronic disease.

The size of the safety database depends on a number of factors, including whether the drug is a new molecular entity (NME) or a reformulation of a known drug substance, the nature of the safety findings from the clinical trials, and the nonclinical data for the drug under development. For the safety evaluation of an NME intended for treatment of alcoholism, we recommend sponsors refer to the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* for drugs intended for long-term treatment of non-life-threatening conditions and to the guidance for industry *Premarketing Risk Assessment*. These guidances make recommendations on the minimum size of the database. A safety database larger than recommended in these guidances may be warranted for a number of reasons (many of which are discussed in these guidances), including safety signals emerging as more clinical data become available.

For reformulations of drugs with existing alcoholism indications, the size of the safety database should reflect the differences from existing formulations of the drug and the gap in safety data expected from these differences. In general, in the case of reformulated drugs, the amount of safety data that should be collected to support safe use depends on differences in pharmacokinetics and route of administration. To determine an appropriate number of patients for the safety database for a drug previously approved for an alcoholism indication, or other indication, sponsors should consider the extent of differences between the previous patient population studied and the alcoholism population under evaluation, and whether the differences alter the risk for adverse reactions.

B. Specific Efficacy Trial Considerations

1. Trial Design

Alcoholism clinical trials should be designed as randomized, placebo-controlled, superiority trials with a minimum duration of 6 months and a primary endpoint based on the response rate. Responders can be defined either as patients who do not drink at all during the observation period, or as patients who do not have any heavy drinking days during the observation period. A responder analysis is recommended because calculations of group mean values such as percent days abstinent or percent of heavy drinking days across a treatment group are difficult to interpret with respect to the clinical benefit for individual patients. Responder analyses illustrate the clinically important effect of a treatment in an individualized fashion, and facilitate risk-

benefit comparisons. Responder analyses also may reveal the effect of a drug that has a clinically important effect in a small subset of patients.

The primary endpoint and responder definition were chosen based on unpublished analyses commissioned by NIAAA of longitudinal data from both clinical trial settings and observational settings. Patients who never exceeded the heavy drinking limits had minimal alcohol-related consequences and were much less likely to have relapsed at follow-up.

Abstinence also can be used as a responder definition for the primary endpoint.

The recommended trial duration is based on data indicating that drinking patterns over shorter durations of time, such as 12 weeks, may not be stable or representative of future experience (Zweben and Cisler 2003) and may be too brief to predict ongoing treatment response. It is acknowledged that many other chronic diseases are studied in trials of only 3 months' (12 weeks') duration using *direct* measures of clinical benefit. However, the problems associated with alcoholism are not readily reversible with cessation of drinking or with the avoidance of heavy drinking. Sustained adherence to the target change in drinking behavior, an *indirect* measure, is needed to accrue clinical benefit.

It is also understood that periods of abstinence are quite common among alcohol-dependent individuals: in one survey (Schuckit, Tipp, et al. 1997), periods of abstinence lasting at least 3 months were reported by 62.3 percent. This could make it hard to show a treatment effect in a brief alcoholism treatment trial.

Some might suggest that trials of 1 year's duration would be more appropriate. In the alcoholism field, the duration of abstinence considered to represent a stable condition, or sustained remission, is often set at 12 months.[7] Once well-established, abstinence from alcohol appears, for many patients, to be a stable pattern, sustained over several years of follow-up (Dawson, Goldstein, et al. 2007). However, based on data indicating that abstinence at 6 months has been shown to be a predictor of abstinence at 5-year follow-up (Weisner, Ray, et al. 2003), and in the interest of practicality, we recommend trials with a minimum of 6 months on-treatment observation.

Neither abstinence nor no heavy drinking responder definitions need any additional data to support the pattern of drinking behavior as a valid surrogate for clinical benefit.

Sponsors can choose other definitions of treatment responders, but would need to submit data that demonstrate the target drinking pattern they select is a valid surrogate for clinical benefit.

2. Trial Population

The trial population should be patients with alcoholism who require pharmacologic treatment. The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria are commonly used to define addiction populations. However, the latest version of the DSM (DSM-V) subsumes all

[7] Diagnostic and Statistical Manual of Mental Disorders, 2000, Fourth Edition, Text Revision (DSM-IV-TR), American Psychiatric Publishing, Inc.

problematic use of alcohol under the term *alcohol use disorders (AUD)*. The blanket designation of AUD introduces ambiguity with respect to defining a trial population for alcoholism clinical trials, because patients with mild or early alcohol use problems would be included if all patients with DSM-V AUD were enrolled. Therefore, sponsors should create eligibility criteria adequate to define a population of patients with a degree of AUD severity that may benefit from pharmacologic treatment. The DSM diagnostic criteria for AUD can be used as a foundation, augmented by other key factors that would identify that set of patients with AUD for whom pharmacologic treatment would be appropriate. These might include a requirement that particular DSM-V diagnostic criteria are met, or that other features are present, such as a subjective loss of control over drinking.

It is important to highlight that patients with mild degrees of AUD are likely to benefit from nonpharmacologic interventions and are therefore not the target population for drugs to treat alcoholism. This means both that the risk-benefit calculation is different for these patients than for those who are in need of pharmacologic treatment, and that they may have a high rate of placebo response that can complicate the demonstration of efficacy in clinical trials. Thus, we recommend that patients whose problems fall into the category of *mild alcohol use disorder*, some patients who would meet criteria for *moderate alcohol use disorder*, or those who are perceived to have a problem of *abuse* but not *addiction*, are not generally the ideal population for study.

3. Entry Criteria

Patients should have a history of episodes of heavy drinking in the period before screening that would permit detection of a change in drinking behavior in this regard as a result of pharmacotherapy. Patients with a history suggestive of clinically significant withdrawal symptoms can be enrolled, but the protocol should include procedures to monitor for withdrawal and to provide necessary treatment.

The decision to enroll patients who are drinking at baseline or patients who have ceased drinking at the time of enrollment should be based on the presumed mechanism of action of the drug. Some drugs may be hypothesized to be effective in helping patients to stop drinking by blocking the effects of alcohol (i.e., via extinction of the behavior). Other drugs might be useful in reducing the risk of relapse once drinking has ceased.

4. Special Populations

Patients with a range of comorbid conditions typically seen in patients with alcoholism, including hepatic impairment, should be enrolled in clinical trials.

5. Choice of Comparators

Sponsors should use placebo comparators. An active comparator also can be included in the trial. Claims of comparative superiority, however, involve specific planning in trial design to demonstrate that there is a clinically meaningful benefit of the drug in question over the

comparator. The comparator drug should be used in an effective dose and in an appropriate population to support a comparative claim.

6. Efficacy Endpoints

Trials should measure the proportion of patients in each treatment group who attain, and sustain over the observation period, a target drinking pattern that is considered a valid surrogate for clinical benefit. The following two options can be used as target drinking patterns and do not need any additional data to support the pattern as a valid surrogate for clinical benefit. Sponsors should discuss other options with the division.

(1) **Abstinence.** As noted above, trials that use complete abstinence as the target drinking pattern can be used.

(2) **No Heavy Drinking.** Trials that use no heavy drinking as the target drinking pattern can be used. This is based on several lines of evidence that provide support for this pattern as a valid surrogate for clinical benefit. Several of these lines of support are from unpublished analyses, but there are also published studies that confirm these analyses. Support for this endpoint is summarized in Appendix 2.

7. Endpoint Adjudication

Information about patients' drinking can be collected using the Time-Line Follow-Back Method (TLFB) (Sobell, Maisto, et al. 1979). Briefly, the TLFB is a calendar-assisted retrospective reconstruction of how many drinks were consumed per day. Initially, the TLFB was developed to be administered by a research assistant, but other techniques including computer-based administration have also been developed. The retrospective window is as long as 3 months. It is generally understood that the TLFB data are not a precise reflection of a patient's drinking, but the TLFB has been widely accepted as providing a reasonable estimate that is sensitive to change.

Note that if sponsors are interested in documenting only abstinence versus any drinking, or adherence to nonheavy limits versus any violation of heavy drinking limits, it may not be necessary to use the TLFB method of reconstruction of drinking day by day. Other methods may be sufficient for obtaining the information necessary to adjudicate the patient as a responder or nonresponder. For example, the Alcohol Research Group/National Alcohol Research Center's 2009 – 2010 National Alcohol Survey[8] used the following question: "Think of all kinds of alcoholic beverages combined, that is, any combination of bottles or cans of beer, glasses of wine, drinks containing liquor of any kind, or coolers, flavored malt beverages or pre-made cocktails. In this question, 1 drink is equal to a 12 ounce bottle or can of beer or cooler, a five ounce glass of wine, or a 1 shot of liquor (1.5 ounces). During the last 12 months, what is the largest number of drinks you had on any single day?".

Either self-report method should be supplemented by some type of biological verification. Currently, there are no ideal biomarkers of drinking that can be used to reliably capture any

[8] http://www.arg.org/downloads/arg/N12%20FINAL%20Landline%20Questionnaire.pdf (accessed 4/25/14)

instance of drinking or of heavy drinking, but some attempt to collect biological data may have the effect of increasing the veracity of self-report. Additionally, patients who are acutely intoxicated cannot give reliable retrospective accounts. Therefore, at a minimum, a breath alcohol measurement at each visit should be incorporated.

It is recommended that the data on alcohol use be collected by staff who are not providing counseling. This is intended to reduce the likelihood that patients will conceal drinking to avoid disappointing the therapist.

If sponsors are interested in documenting only whether patients are responders or nonresponders, it is not necessary to accurately reconstruct the amount consumed on each day of the trial, and therefore there are methods to ensure that missing data should be relatively rare. A patient who has already had a heavy drinking day during the efficacy ascertainment period is already adjudicated even if lost to follow-up. If a patient who met the responder definition up to the point of dropping out can be located by telephone, he or she can be asked "What is the largest number of drinks you had on any one occasion since the last time we saw you?" If the patient indicates that he or she has had at least one heavy drinking day, the outcome for that patient is adjudicated and is not considered missing. Patients who self-report ongoing adherence to the no heavy drinking limits may present a challenge because of the lack of biological verification or other sources of confirmation of self-report; these patients might be included as either responders or nonresponders in different sensitivity analyses. Only patients who met the responder definition up to the point of loss to follow-up and cannot be located should be considered truly unadjudicated. Careful attention to obtaining contact information at the time of trial enrollment can limit the number of patients for whom outcome data are truly missing.

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APPENDIX 1: TERMINOLOGY RELATED TO PROBLEM ALCOHOL USE

The WHO notes that alcoholism may be considered to be synonymous with *alcohol addiction*, but does not endorse the use of either term. Addiction, per the WHO, is "Repeated use of a psychoactive substance or substances, to the extent that the user (referred to as an addict) is periodically or chronically intoxicated, shows a compulsion to take the preferred substance (or substances), has great difficulty in voluntarily ceasing or modifying substance use, and exhibits determination to obtain psychoactive substances by almost any means. Typically, tolerance is prominent and a withdrawal syndrome frequently occurs when substance use is interrupted."[9]

More recently, the term *alcohol dependence* was substituted for both alcoholism and alcohol addiction in diagnostic criteria by both the WHO and the American Psychiatric Association (APA), because of concerns that the word addiction carried an unwanted stigma, and in turn, could be a barrier to seeking treatment. However, this created ambiguity, because the term *dependence* came to have dual meanings connoting both a physical neuroadaptation (sometimes called *physical dependence*) and the notion of addiction.

Another term, *alcohol abuse* has been applied when individuals use alcohol to the point of experiencing problems caused by drinking, but do not manifest features of alcoholism. Notably, there have been concerns voiced that the term abuse also carries a stigma that would prevent individuals from self-identifying or seeking treatment and suggestions have been made to abandon this term as well, replacing it with *misuse*. For FDA purposes, the terms addiction, dependence, abuse, and misuse are distinct from one another, but we acknowledge that they may be used inconsistently, and sometimes interchangeably. We have retained the historical term, alcoholism, in this guidance because of ambiguity and ongoing evolution in the use of other terms.

In the most recent version of the APA's DSM, a new diagnostic approach subsuming all problematic use of alcohol under the term AUD has been put forth. This construct eliminates the distinction between alcohol abuse and alcohol dependence (the latter term being essentially synonymous with alcohol addiction or alcoholism), and creates a diagnosis for individuals with problems mild enough that they are merely markers for *future* problems related to drinking. This facilitates early identification and intervention, but it also creates a problematic level of heterogeneity in the group of people who meet criteria for the diagnosis of AUD.

[9] http://www.who.int/substance_abuse/terminology/who_lexicon/en

APPENDIX 2: SOURCES PROVIDING SUPPORT FOR NO HEAVY DRINKING AS A VALID SURROGATE FOR CLINICAL BENEFIT

This Appendix summarizes select sources of information that provide support for the distinctive pattern of drinking reduction, referred to as no heavy drinking days in this guidance, as a valid surrogate for clinical benefit.

Project MATCH

The first unpublished analysis, commissioned by the Treatment Research Branch at NIAAA, explored the dataset from Project MATCH, a trial comparing 3 different behavioral (nonpharmacologic) treatments delivered over 12 weeks in 1,726 patients with diagnoses of alcohol abuse or dependence who had been actively drinking in the 3 months before trial entry. Assessments were conducted every 3 months, capturing both alcohol consumption and various measures of drinking-related consequences, and patient function or dysfunction. The analysis examined the relationship of problems and functioning to various measures of drinking.[10] The investigator found a high degree of variability using continuous measures of drinking such as percent days abstinent or drinks per day, but that a consumption quantity cut-off was related strongly to an array of consequences and functioning variables. The conclusion was that the best single predictor of nonconsequential drinking was never exceeding the daily heavy drinking limits. The recommendations based on this analysis were that the target pattern of drinking should be defined as being abstinent or never exceeding three drinks on a single occasion (women) or four drinks on a single occasion (men). In the sample analyzed, 22 percent of patients met this definition over the full 12-month post-treatment follow-up.

If a target drinking pattern based on percent days abstinent was of interest, the analysis suggested that similar functional outcomes would require a pattern of 92 percent days abstinent. Because of high degrees of fluctuations in consumption and status across time, the analysis also suggested that longer follow-up periods (6 to 12 months) were needed to provide insight into more sustained status.

National Alcohol Surveys

The second NIAAA-commissioned analysis used data from the 1995 and 2000 National Alcohol Surveys, which collected information on alcohol consumption using a graduated frequencies measure (Greenfield 2000), alcohol dependence criteria, and information about alcohol-related social consequences. Participants included 7,447 current drinkers, but the analysis focused on the subset of 820 respondents who either reported having had prior treatment for alcohol problems or endorsed a concern about their drinking, to better approximate the target population for alcoholism treatment drugs.

The investigator concluded that treated or concerned drinkers who restrict intake to low volume (averaging fewer than 2 drinks per week) and whose quantities in a day never exceeded

[10] The analysis of the Project MATCH data was conducted by Dr. Ron A. Cisler.

3 (women)/4(men) carry low risk of 12-month dependence or abuse (less than 5 percent).[11] Those drinking 4 plus/5 plus even on occasion have significantly higher risks (10 to 20 percent) of meeting criteria for AUD. The report noted that "If [treated or concerned] individuals drink at all, the only somewhat 'safe' level appears to be drinking less than 2 drinks/week on average and never exceeding 4 drinks for a man or 3 drinks in a day for a woman."

National Epidemiologic Survey on Alcohol and Related Conditions

Findings from two waves of data from the National Epidemiologic Survey on Alcohol and Related Conditions were published by Deborah Dawson and colleagues (Dawson, Goldstein, et al. 2007). Wave 1, collected in 2001 to 2002, identified 4,422 individuals who had met criteria for alcohol dependence *before* the past year. Of these:

- 25.0 percent were still classified as dependent in the past year
- 27.3 percent were classified as being in partial remission
- *11.8 percent were asymptomatic risk drinkers who demonstrated a pattern of drinking that put them at risk of relapse*
- *17.7 percent were low-risk drinkers (no heavy drinking days)*
- *18.2 percent were abstainers*

The last 3 categories comprise 2,109 individuals in full remission from alcohol dependence.

At Wave 2, collected 2004 to 2005, 1,772 of those 2,109 individuals were re-interviewed. Recurrence of AUD symptoms occurred in 51 percent of asymptomatic risk drinkers (any heavy drinking days); 27.2 percent of low-risk drinkers (no heavy drinking days); and 7.3 percent of abstainers. The adjusted odds ratios of recurrence of AUD symptoms compared to abstainers was 14.6 for asymptomatic risk drinkers and 5.8 for low-risk drinkers.

The proportion of individuals who had been in remission at Wave 1 who met criteria for alcohol dependence at Wave 2 was 10.2 percent for asymptomatic risk drinkers (any heavy drinking days); 4 percent for low-risk drinkers (no heavy drinking days); and 2.9 percent for abstainers. The adjusted odds ratios of recurrence of dependence, relative to abstainers, was 7.0 for risk drinkers and 3.0 for low-risk drinkers. Thus, compared to abstinence, no heavy drinking days does still represent three times the risk of relapse to dependence compared to abstinence and nearly six times the risk of relapse to AUD symptoms. However, drinking patterns including any heavy drinking days seem to carry 7 times the risk of relapse to dependence compared to abstinence and nearly 15 times the risk of relapse to AUD symptoms compared to abstinence. Those who engaged in *risk drinking* (equals heavy drinking days) even fewer than 1 time per month at Wave 1 were significantly more likely to meet criteria for dependence at Wave 2 than

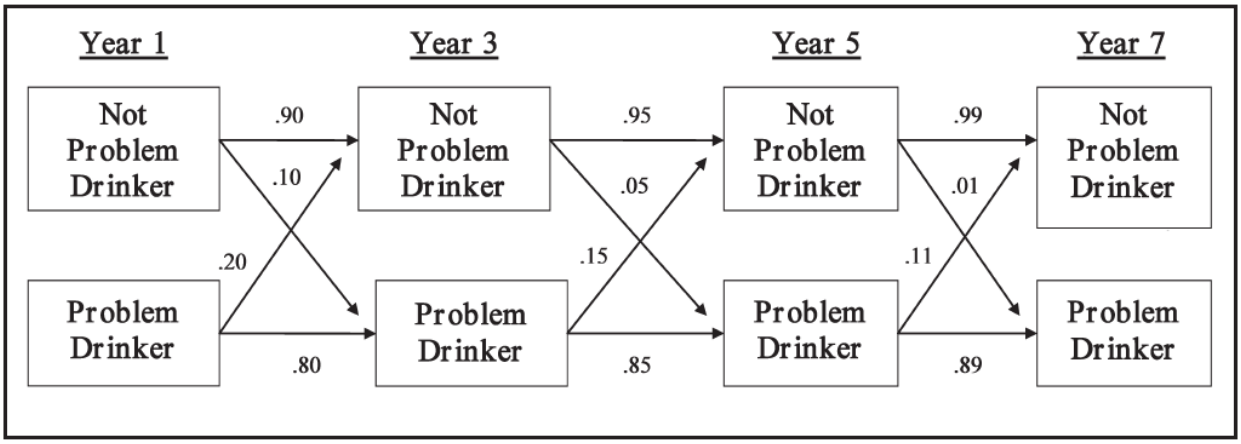
[11] The analysis of National Alcohol Survey data was conducted by Dr. Thomas Greenfield.

those who did not, and there was no association between frequency of risk drinking and the adjusted prospective risks of chronic medical conditions other than liver disease.

Weisner

Delucchi and Weisner (Delucchi and Weisner 2010) examined transitions into and out of problem drinking across 7 years in a longitudinal study of 1,350 problem drinkers sampled from one county's general population (general population sample) and individuals entering the county's public and private chemical dependency programs (treatment sample). Problem drinking was defined as 2 or more of the following in the previous 12 months: (1) 5 plus drinks per day at least once a month for men or 3 plus drinks in a day weekly for women; (2) 1 or more alcohol-related social consequences (from a list of 8); and (3) 1 or more alcohol dependence symptoms (from a list of 9). Follow-up interviews were conducted 1, 3, 5, and 7 years after baseline. The extent to which problem drinkers transition into and out of problem drinking was examined using Markov modeling.

The authors reported that a latent Markov model with heterogeneous transitions and five patterns fit the data, and the estimated transition probabilities are displayed in the following figure found in the article.



Source: Delucchi and Weisner, 2010, p. 215.

The authors demonstrated that individuals transitioning into a status of nonproblem drinker are likely to remain in that status over time. Conversely, if individuals maintain a problem drinker status over time, it becomes increasingly difficult to transition out of that status.

Sanchez-Craig

Data from three independent trials involving two distinct populations of problem drinkers were pooled with the intent of refining guidelines on moderate drinking for heavy drinkers (Sanchez-Craig, Wilkinson, et al. 1995). The trial patients were 235 individuals who participated in 3 trials of secondary prevention of alcohol problems and were interviewed at the 12-month follow-up period. Patients were classified as problem-free (reporting no alcohol-related problems in the past 6 or 9 months) or problem (reporting 1 or more problems). In the problem-free group, the average number of drinks per day and the upper limit of the confidence interval were less than

four. For the group reporting a problem, the mean quantity per day drinking was 5.5. The authors also conducted an analysis grouping patients at 12-month follow-up into 4 categories based on both the amount of drinks consumed per day and the frequency of drinking in a week. The authors concluded that the two groups above the cutoff on quantity of drinks per day (i.e., five or more for men and four or more for women) had similar prevalence of all problem types and higher prevalence, while the two groups below this cutoff experienced a low likelihood of problems. This is an additional source of support that was already available at the time that NIAAA had commissioned the formerly described analyses.