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# 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## *DRAFT GUIDANCE*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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# Alcoholism: Developing Drugs for Treatment Guidance for Industry

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**U.S. Department of Health and Human Services  
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1 **Alcoholism: Developing Drugs for Treatment**  
2 **Guidance for Industry<sup>1</sup>**  
3  
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5

6  
7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current  
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to  
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of  
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA  
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call  
12 the appropriate number listed on the title page of this guidance.  
13

14  
15  
16  
17 **I. INTRODUCTION**  
18

19 The purpose of this guidance is to assist sponsors in the clinical development of drugs for the  
20 treatment of alcoholism.<sup>2</sup> There are many different terms, definitions, and diagnostic criteria that  
21 have been used to describe this condition. However, in this guidance, we use the term  
22 *alcoholism* to describe patients with alcohol use problems that would make them candidates for  
23 treatment with medication. As the World Health Organization (WHO) notes,<sup>3</sup> alcoholism is a  
24 "term of long-standing use" and is "generally taken to refer to chronic continual drinking or  
25 periodic consumption of alcohol which is characterized by impaired control over drinking,  
26 frequent episodes of intoxication, and preoccupation with alcohol and the use of alcohol despite  
27 adverse consequences." Further discussion of terminology can be found in Appendix 1.  
28

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

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<sup>1</sup> 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.

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

<sup>3</sup> [http://www.who.int/substance\\_abuse/terminology/who\\_lexicon/en/](http://www.who.int/substance_abuse/terminology/who_lexicon/en/) (accessed 2/1/14)

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36 Addiction Products (DAAAP), pharmaceutical sponsors, the academic community, and the  
37 public.<sup>4</sup>

38  
39 This guidance does not contain discussion of the general issues of statistical analysis or clinical  
40 trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*  
41 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*  
42 *Trials*, respectively.<sup>5</sup>

43  
44 FDA’s guidance documents, including this guidance, do not establish legally enforceable  
45 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should  
46 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
47 cited. The use of the word *should* in Agency guidances means that something is suggested or  
48 recommended, but not required.

49  
50

51 **II. DEVELOPMENT PROGRAM**

52

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

66

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

---

<sup>4</sup> 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.

<sup>5</sup> 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>.

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

81

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

86

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

91

**A. General Considerations**

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**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),<sup>6</sup> 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.

---

<sup>6</sup> 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.

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115           3.     *Efficacy Considerations*

116  
117     Generally, two adequate and well-controlled trials will be needed to support an efficacy claim for  
118     this indication.

120           4.     *Safety Considerations*

121  
122     The safety database should be sufficiently sized, from both the standpoint of sample size and  
123     length of observation, to assess the safety of a drug intended for the treatment of a chronic  
124     disease.

125  
126     The size of the safety database depends on a number of factors, including whether the drug is a  
127     new molecular entity (NME) or a reformulation of a known drug substance, the nature of the  
128     safety findings from the clinical trials, and the nonclinical data for the drug under development.  
129     For the safety evaluation of an NME intended for treatment of alcoholism, we recommend  
130     sponsors refer to the ICH guidance for industry *E1A The Extent of Population Exposure to*  
131     *Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening*  
132     *Conditions* for drugs intended for long-term treatment of non-life-threatening conditions and to  
133     the guidance for industry *Premarketing Risk Assessment*. These guidances make  
134     recommendations on the minimum size of the database. A safety database larger than  
135     recommended in these guidances may be warranted for a number of reasons (many of which are  
136     discussed in these guidances), including safety signals emerging as more clinical data become  
137     available.

138  
139     For reformulations of drugs with existing alcoholism indications, the size of the safety database  
140     should reflect the differences from existing formulations of the drug and the gap in safety data  
141     expected from these differences. In general, in the case of reformulated drugs, the amount of  
142     safety data that should be collected to support safe use depends on differences in  
143     pharmacokinetics and route of administration. To determine an appropriate number of patients  
144     for the safety database for a drug previously approved for an alcoholism indication, or other  
145     indication, sponsors should consider the extent of differences between the previous patient  
146     population studied and the alcoholism population under evaluation, and whether the differences  
147     alter the risk for adverse reactions.

148  
149           **B.     Specific Efficacy Trial Considerations**

150  
151           1.     *Trial Design*

152  
153     Alcoholism clinical trials should be designed as randomized, placebo-controlled, superiority  
154     trials with a minimum duration of 6 months and a primary endpoint based on the response rate.  
155     Responders can be defined either as patients who do not drink at all during the observation  
156     period, or as patients who do not have any heavy drinking days during the observation period. A  
157     responder analysis is recommended because calculations of group mean values such as percent  
158     days abstinent or percent of heavy drinking days across a treatment group are difficult to  
159     interpret with respect to the clinical benefit for individual patients. Responder analyses illustrate  
160     the clinically important effect of a treatment in an individualized fashion, and facilitate risk-

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

163  
164 The primary endpoint and responder definition were chosen based on unpublished analyses  
165 commissioned by NIAAA of longitudinal data from both clinical trial settings and observational  
166 settings. Patients who never exceeded the heavy drinking limits had minimal alcohol-related  
167 consequences and were much less likely to have relapsed at follow-up.

168  
169 Abstinence also can be used as a responder definition for the primary endpoint.

170  
171 The recommended trial duration is based on data indicating that drinking patterns over shorter  
172 durations of time, such as 12 weeks, may not be stable or representative of future experience  
173 (Zweben and Cisler 2003) and may be too brief to predict ongoing treatment response. It is  
174 acknowledged that many other chronic diseases are studied in trials of only 3 months' (12  
175 weeks') duration using *direct* measures of clinical benefit. However, the problems associated  
176 with alcoholism are not readily reversible with cessation of drinking or with the avoidance of  
177 heavy drinking. Sustained adherence to the target change in drinking behavior, an *indirect*  
178 measure, is needed to accrue clinical benefit.

179  
180 It is also understood that periods of abstinence are quite common among alcohol-dependent  
181 individuals: in one survey (Schuckit, Tipp, et al. 1997), periods of abstinence lasting at least 3  
182 months were reported by 62.3 percent. This could make it hard to show a treatment effect in a  
183 brief alcoholism treatment trial.

184  
185 Some might suggest that trials of 1 year's duration would be more appropriate. In the alcoholism  
186 field, the duration of abstinence considered to represent a stable condition, or sustained  
187 remission, is often set at 12 months.<sup>7</sup> Once well-established, abstinence from alcohol appears,  
188 for many patients, to be a stable pattern, sustained over several years of follow-up (Dawson,  
189 Goldstein, et al. 2007). However, based on data indicating that abstinence at 6 months has been  
190 shown to be a predictor of abstinence at 5-year follow-up (Weisner, Ray, et al. 2003), and in the  
191 interest of practicality, we recommend trials with a minimum of 6 months on-treatment  
192 observation.

193  
194 Neither abstinence nor no heavy drinking responder definitions need any additional data to  
195 support the pattern of drinking behavior as a valid surrogate for clinical benefit.

196  
197 Sponsors can choose other definitions of treatment responders, but would need to submit data  
198 that demonstrate the target drinking pattern they select is a valid surrogate for clinical benefit.

199  
200 **2. Trial Population**

201  
202 The trial population should be patients with alcoholism who require pharmacologic treatment.  
203 The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria are commonly used to  
204 define addiction populations. However, the latest version of the DSM (DSM-V) subsumes all

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



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

215  
216 It is important to highlight that patients with mild degrees of AUD are likely to benefit from  
217 nonpharmacologic interventions and are therefore not the target population for drugs to treat  
218 alcoholism. This means both that the risk-benefit calculation is different for these patients than  
219 for those who are in need of pharmacologic treatment, and that they may have a high rate of  
220 placebo response that can complicate the demonstration of efficacy in clinical trials. Thus, we  
221 recommend that patients whose problems fall into the category of *mild alcohol use disorder*,  
222 some patients who would meet criteria for *moderate alcohol use disorder*, or those who are  
223 perceived to have a problem of *abuse* but not *addiction*, are not generally the ideal population for  
224 study.

225  
226 **3. *Entry Criteria***

227  
228 Patients should have a history of episodes of heavy drinking in the period before screening that  
229 would permit detection of a change in drinking behavior in this regard as a result of  
230 pharmacotherapy. Patients with a history suggestive of clinically significant withdrawal  
231 symptoms can be enrolled, but the protocol should include procedures to monitor for withdrawal  
232 and to provide necessary treatment.

233  
234 The decision to enroll patients who are drinking at baseline or patients who have ceased drinking  
235 at the time of enrollment should be based on the presumed mechanism of action of the drug.  
236 Some drugs may be hypothesized to be effective in helping patients to stop drinking by blocking  
237 the effects of alcohol (i.e., via extinction of the behavior). Other drugs might be useful in  
238 reducing the risk of relapse once drinking has ceased.

239  
240 **4. *Special Populations***

241  
242 Patients with a range of comorbid conditions typically seen in patients with alcoholism,  
243 including hepatic impairment, should be enrolled in clinical trials.

244  
245 **5. *Choice of Comparators***

246  
247 Sponsors should use placebo comparators. An active comparator also can be included in the  
248 trial. Claims of comparative superiority, however, involve specific planning in trial design to  
249 demonstrate that there is a clinically meaningful benefit of the drug in question over the

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

252

253           6.       *Efficacy Endpoints*

254

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

260

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

263

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

269

270           7.       *Endpoint Adjudication*

271

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

280

281 Note that if sponsors are interested in documenting only abstinence versus any drinking, or  
282 adherence to nonheavy limits versus any violation of heavy drinking limits, it may not be  
283 necessary to use the TLFB method of reconstruction of drinking day by day. Other methods may  
284 be sufficient for obtaining the information necessary to adjudicate the patient as a responder or  
285 nonresponder. For example, the Alcohol Research Group/National Alcohol Research Center's  
286 2009 – 2010 National Alcohol Survey<sup>8</sup> used the following question: "Think of all kinds of  
287 alcoholic beverages combined, that is, any combination of bottles or cans of beer, glasses of  
288 wine, drinks containing liquor of any kind, or coolers, flavored malt beverages or pre-made  
289 cocktails. In this question, 1 drink is equal to a 12 ounce bottle or can of beer or cooler, a five  
290 ounce glass of wine, or a 1 shot of liquor (1.5 ounces). During the last 12 months, what is the  
291 largest number of drinks you had on any single day?"

292

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

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

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295 instance of drinking or of heavy drinking, but some attempt to collect biological data may have  
296 the effect of increasing the veracity of self-report. Additionally, patients who are acutely  
297 intoxicated cannot give reliable retrospective accounts. Therefore, at a minimum, a breath  
298 alcohol measurement at each visit should be incorporated.  
299

300 It is recommended that the data on alcohol use be collected by staff who are not providing  
301 counseling. This is intended to reduce the likelihood that patients will conceal drinking to avoid  
302 disappointing the therapist.  
303

304 If sponsors are interested in documenting only whether patients are responders or nonresponders,  
305 it is not necessary to accurately reconstruct the amount consumed on each day of the trial, and  
306 therefore there are methods to ensure that missing data should be relatively rare. A patient who  
307 has already had a heavy drinking day during the efficacy ascertainment period is already  
308 adjudicated even if lost to follow-up. If a patient who met the responder definition up to the  
309 point of dropping out can be located by telephone, he or she can be asked “What is the largest  
310 number of drinks you had on any one occasion since the last time we saw you?” If the patient  
311 indicates that he or she has had at least one heavy drinking day, the outcome for that patient is  
312 adjudicated and is not considered missing. Patients who self-report ongoing adherence to the no  
313 heavy drinking limits may present a challenge because of the lack of biological verification or  
314 other sources of confirmation of self-report; these patients might be included as either responders  
315 or nonresponders in different sensitivity analyses. Only patients who met the responder  
316 definition up to the point of loss to follow-up and cannot be located should be considered truly  
317 unadjudicated. Careful attention to obtaining contact information at the time of trial enrollment  
318 can limit the number of patients for whom outcome data are truly missing.  
319

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**REFERENCES**

- 320  
321  
322 Dawson, DA, RB Goldstein, and BF Grant, 2007, Rates and Correlates of Relapse Among  
323 Individuals in Remission From DSM-IV Alcohol Dependence: A 3-Year Follow-Up, Alcohol  
324 Clin Exp. Res., 31, 2036-2045.  
325  
326 Delucchi, KL and C Weisner, 2010, Transitioning Into and Out of Problem Drinking Across  
327 Seven Years, J Stud. Alcohol Drugs, 71, 210-218.  
328  
329 Greenfield, TK, 2000, Ways of Measuring Drinking Patterns and the Difference They Make:  
330 Experience with Graduated Frequencies, J Subst. Abuse, 12, 33-49.  
331  
332 Sanchez-Craig, M, DA Wilkinson, and R Davila, 1995, Empirically Based Guidelines for  
333 Moderate Drinking: 1-Year Results From Three Studies With Problem Drinkers, Am. J Public  
334 Health, 85, 823-828.  
335  
336 Schuckit, MA, JE Tipp, TL Smith, and KK Bucholz, 1997, Periods of Abstinence Following the  
337 Onset of Alcohol Dependence in 1,853 Men and Women, J Stud. Alcohol, 58, 581-589.  
338  
339 Sobell, LC, SA Maisto, MB Sobell, and AM Cooper, 1979, Reliability of Alcohol Abusers' Self-  
340 Reports of Drinking Behavior, Behav. Res. Ther., 17, 157-160.  
341  
342 Weisner, C, GT Ray, JR Mertens, DD Satre, and C Moore, 2003, Short-Term Alcohol and Drug  
343 Treatment Outcomes Predict Long-Term Outcome, Drug Alcohol Depend., 71, 281-294.  
344  
345 Zweben, A and RA Cisler, 2003, Clinical and Methodological Utility of a Composite Outcome  
346 Measure for Alcohol Treatment Research, Alcohol Clin Exp. Res., 27, 1680-1685.  
347

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348           **APPENDIX 1: TERMINOLOGY RELATED TO PROBLEM ALCOHOL USE**

349

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

357

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

364

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

374

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

382

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<sup>9</sup> [http://www.who.int/substance\\_abuse/terminology/who\\_lexicon/en](http://www.who.int/substance_abuse/terminology/who_lexicon/en)

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383           **APPENDIX 2: SOURCES PROVIDING SUPPORT FOR NO HEAVY DRINKING**  
384                           **AS A VALID SURROGATE FOR CLINICAL BENEFIT**  
385

386       This Appendix summarizes select sources of information that provide support for the distinctive  
387       pattern of drinking reduction, referred to as no heavy drinking days in this guidance, as a valid  
388       surrogate for clinical benefit.  
389

390       **Project MATCH**

391  
392       The first unpublished analysis, commissioned by the Treatment Research Branch at NIAAA,  
393       explored the dataset from Project MATCH, a trial comparing 3 different behavioral  
394       (nonpharmacologic) treatments delivered over 12 weeks in 1,726 patients with diagnoses of  
395       alcohol abuse or dependence who had been actively drinking in the 3 months before trial entry.  
396       Assessments were conducted every 3 months, capturing both alcohol consumption and various  
397       measures of drinking-related consequences, and patient function or dysfunction. The analysis  
398       examined the relationship of problems and functioning to various measures of drinking.<sup>10</sup> The  
399       investigator found a high degree of variability using continuous measures of drinking such as  
400       percent days abstinent or drinks per day, but that a consumption quantity cut-off was related  
401       strongly to an array of consequences and functioning variables. The conclusion was that the best  
402       single predictor of nonconsequential drinking was never exceeding the daily heavy drinking  
403       limits. The recommendations based on this analysis were that the target pattern of drinking  
404       should be defined as being abstinent or never exceeding three drinks on a single occasion  
405       (women) or four drinks on a single occasion (men). In the sample analyzed, 22 percent of  
406       patients met this definition over the full 12-month post-treatment follow-up.  
407

408       If a target drinking pattern based on percent days abstinent was of interest, the analysis suggested  
409       that similar functional outcomes would require a pattern of 92 percent days abstinent. Because  
410       of high degrees of fluctuations in consumption and status across time, the analysis also suggested  
411       that longer follow-up periods (6 to 12 months) were needed to provide insight into more  
412       sustained status.  
413

414       **National Alcohol Surveys**

415  
416       The second NIAAA-commissioned analysis used data from the 1995 and 2000 National Alcohol  
417       Surveys, which collected information on alcohol consumption using a graduated frequencies  
418       measure (Greenfield 2000), alcohol dependence criteria, and information about alcohol-related  
419       social consequences. Participants included 7,447 current drinkers, but the analysis focused on  
420       the subset of 820 respondents who either reported having had prior treatment for alcohol  
421       problems or endorsed a concern about their drinking, to better approximate the target population  
422       for alcoholism treatment drugs.  
423

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

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<sup>10</sup> The analysis of the Project MATCH data was conducted by Dr. Ron A. Cisler.

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426 3 (women)/4(men) carry low risk of 12-month dependence or abuse (less than 5 percent).<sup>11</sup>  
427 Those drinking 4 plus/5 plus even on occasion have significantly higher risks (10 to 20 percent)  
428 of meeting criteria for AUD. The report noted that “If [treated or concerned] individuals drink at  
429 all, the only somewhat ‘safe’ level appears to be drinking less than 2 drinks/week on average and  
430 never exceeding 4 drinks for a man or 3 drinks in a day for a woman.”  
431

432 **National Epidemiologic Survey on Alcohol and Related Conditions**  
433

434 Findings from two waves of data from the National Epidemiologic Survey on Alcohol and  
435 Related Conditions were published by Deborah Dawson and colleagues (Dawson, Goldstein, et  
436 al. 2007). Wave 1, collected in 2001 to 2002, identified 4,422 individuals who had met criteria  
437 for alcohol dependence *before* the past year. Of these:  
438

- 439 • 25.0 percent were still classified as dependent in the past year
- 440
- 441 • 27.3 percent were classified as being in partial remission
- 442
- 443 • *11.8 percent were asymptomatic risk drinkers who demonstrated a pattern of drinking*  
444 *that put them at risk of relapse*
- 445
- 446 • *17.7 percent were low-risk drinkers (no heavy drinking days)*  
447
- 448 • *18.2 percent were abstainers*  
449

450 The last 3 categories comprise 2,109 individuals in full remission from alcohol dependence.  
451

452 At Wave 2, collected 2004 to 2005, 1,772 of those 2,109 individuals were re-interviewed.  
453 Recurrence of AUD symptoms occurred in 51 percent of asymptomatic risk drinkers (any heavy  
454 drinking days); 27.2 percent of low-risk drinkers (no heavy drinking days); and 7.3 percent of  
455 abstainers. The adjusted odds ratios of recurrence of AUD symptoms compared to abstainers  
456 was 14.6 for asymptomatic risk drinkers and 5.8 for low-risk drinkers.  
457

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

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<sup>11</sup> The analysis of National Alcohol Survey data was conducted by Dr. Thomas Greenfield.



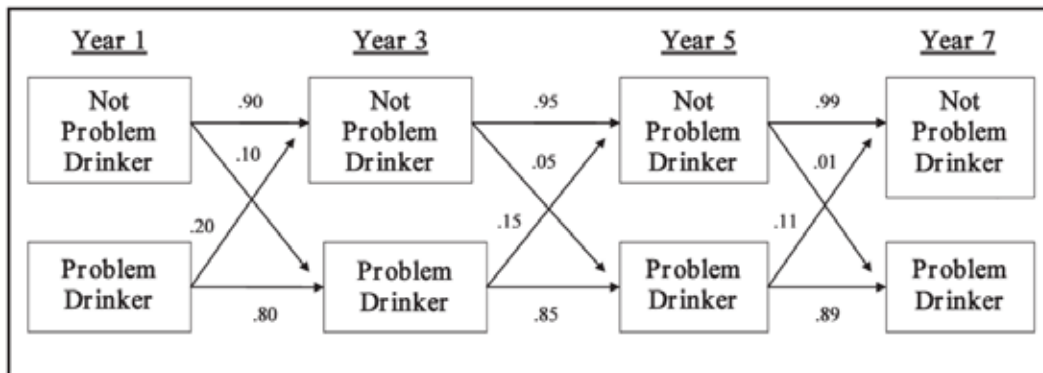
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469 those who did not, and there was no association between frequency of risk drinking and the  
 470 adjusted prospective risks of chronic medical conditions other than liver disease.

471  
 472 **Weisner**

473  
 474 Delucchi and Weisner (Delucchi and Weisner 2010) examined transitions into and out of  
 475 problem drinking across 7 years in a longitudinal study of 1,350 problem drinkers sampled from  
 476 one county’s general population (general population sample) and individuals entering the  
 477 county’s public and private chemical dependency programs (treatment sample). Problem  
 478 drinking was defined as 2 or more of the following in the previous 12 months: (1) 5 plus drinks  
 479 per day at least once a month for men or 3 plus drinks in a day weekly for women; (2) 1 or more  
 480 alcohol-related social consequences (from a list of 8); and (3) 1 or more alcohol dependence  
 481 symptoms (from a list of 9). Follow-up interviews were conducted 1, 3, 5, and 7 years after  
 482 baseline. The extent to which problem drinkers transition into and out of problem drinking was  
 483 examined using Markov modeling.

484  
 485 The authors reported that a latent Markov model with heterogeneous transitions and five patterns  
 486 fit the data, and the estimated transition probabilities are displayed in the following figure found  
 487 in the article.  
 488



489  
 490 **Source:** Delucchi and Weisner, 2010, p. 215.

491  
 492 The authors demonstrated that individuals transitioning into a status of nonproblem drinker are  
 493 likely to remain in that status over time. Conversely, if individuals maintain a problem drinker  
 494 status over time, it becomes increasingly difficult to transition out of that status.

495  
 496 **Sanchez-Craig**

497  
 498 Data from three independent trials involving two distinct populations of problem drinkers were  
 499 pooled with the intent of refining guidelines on moderate drinking for heavy drinkers (Sanchez-  
 500 Craig, Wilkinson, et al. 1995). The trial patients were 235 individuals who participated in 3  
 501 trials of secondary prevention of alcohol problems and were interviewed at the 12-month follow-  
 502 up period. Patients were classified as problem-free (reporting no alcohol-related problems in the  
 503 past 6 or 9 months) or problem (reporting 1 or more problems). In the problem-free group, the  
 504 average number of drinks per day and the upper limit of the confidence interval were less than



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505 four. For the group reporting a problem, the mean quantity per day drinking was 5.5. The  
506 authors also conducted an analysis grouping patients at 12-month follow-up into 4 categories  
507 based on both the amount of drinks consumed per day and the frequency of drinking in a week.  
508 The authors concluded that the two groups above the cutoff on quantity of drinks per day (i.e.,  
509 five or more for men and four or more for women) had similar prevalence of all problem types  
510 and higher prevalence, while the two groups below this cutoff experienced a low likelihood of  
511 problems. This is an additional source of support that was already available at the time that  
512 NIAAA had commissioned the formerly described analyses.  
513