Do Clinical Trials of Treatment of Alcohol Dependence Adequately Enroll Participants With Co-Occurring Independent Mood and Anxiety Disorders? An Analysis of Data From the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Nicolas Hoertel, MD; Bruno Falissard, MD, PhD; Keith Humphreys, PhD; Philip Gorwood, MD, PhD; Anne-Sophie Seigneurie, MD; and Frédéric Limosin, MD, PhD

ABSTRACT

Background: In the care of alcohol-dependent patients, co-occurring independent (ie, not substance-induced) mood and anxiety disorders present a significant challenge. Clinical trials of alcohol dependence treatment could help clinicians meet this challenge, but only if they enroll such complex patients. This study examined whether such individuals are likely to be included in alcohol dependence treatment trials under typical eligibility criteria.

Method: Data were derived from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a national representative sample of 43,093 adults in the United States population. Psychiatric diagnoses were made according to the *DSM-IV* criteria with the Alcohol Use Disorder and Associated Disabilities Interview Schedule—*DSM-IV* Version (AUDADIS-IV).

Results: Of 1,484 alcohol-dependent participants, 39.22% (SE = 1.67) had a co-occurring independent mood or anxiety disorder; more than 60% of these individuals would be ineligible for an alcohol dependence treatment trial under typical eligibility criteria. Alcohol-dependent individuals with current major depressive episode, mania, dysthymia, panic disorder, and generalized anxiety disorder were particularly likely to be excluded from clinical trials. In a subsample of 185 individuals who had sought alcohol treatment, 52.59% (SE = 4.42) had an independent mood or anxiety disorder. Remarkably, almost all of these individuals (96.93%, SE = 1.97) would have been ineligible for clinical trials.

Conclusions: Independent mood and anxiety disorders are prevalent in the alcohol-dependent population but not in clinical trial research samples. For alcohol dependence treatment trials to adequately inform clinical practice, the enrollment of patients with co-occurring mood or anxiety disorders must be increased, through trials tailored to this population, a general relaxation of overly stringent eligibility criteria, or both.

J Clin Psychiatry 2014;75(3):231–237

Submitted: *February 13, 2013; accepted July 12, 2013.*
Online ahead of print: *February 4, 2014 (doi:10.4088/JCP.13m08424).*
Corresponding author: *Nicolas Hoertel, MD, Hôpital Corentin-Celton, 4 parvis Corentin Celton, 92130 Issy-les-Moulineaux, France (nico.hoertel@yahoo.fr).*

Growing evidence indicates that restrictive eligibility criteria used in randomized controlled trials (RCTs) significantly diminish external validity (ie, applicability of clinical trial results to routine clinical care)[1–4] and thereby help perpetuate the gap between research and clinical practice.[5] As with other areas of psychiatric treatment research,[3,6] RCTs for alcohol dependence treatment typically apply numerous eligibility criteria that exclude patients with a variety of psychiatric and medical comorbidities and social characteristics (eg, homelessness) in the hopes of reducing study costs, ensuring the safety of vulnerable patients, complying with regulatory requirements, and decreasing heterogeneity in response to treatment (and thereby increase statistical power).[7,8] However, eligibility criteria are not always well justified.[9] In addition, recent findings in the alcohol field indicate that these widely used eligibility criteria in RCTs for alcohol dependence exclude a large proportion of patients from research participation and could result in a sampling bias.[7,8,10–12] They may not even yield their intended benefits: highly selective studies may require longer recruitment, raising study cost, and criteria intended to reduce heterogeneity in treatment response may have the reverse effect, thereby reducing rather than increasing statistical power.[10] As a result, concerns have emerged regarding the relevance of RCT results to typical patients in community settings.

Adults with alcohol dependence are a highly heterogeneous group.[13] An important source of heterogeneity in treatment response are comorbid psychiatric problems.[14–16] One prevalent example is independent mood and anxiety disorders. Using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which is also analyzed in the present study, Grant and colleagues[17] reported that of the 1,484 individuals with a current diagnosis of alcohol dependence, 430 (27.55%, SE = 1.53) had a current independent mood disorder and 324 (23.45%, SE = 1.42) a current independent anxiety disorder. In the subsample of individuals who had sought treatment (n = 185), prevalences of any current independent mood disorder and any current independent anxiety disorder rose, respectively, to 41.47% (SE = 4.34, N = 78) and 36.20% (SE = 4.27, N = 57). Mounting evidence underscores that treatment for mood and anxiety disorders should not be withheld from individuals with alcohol use disorders in stable remission on the assumption that most of these disorders are due to intoxication or withdrawal.[17] Left untreated, such mood disorders have been shown to lead to relapse of alcohol dependence[18] and increased suicide risk.[17] In addition, independent mood and anxiety disorders,

particularly among individuals who have a comorbid alcohol use disorder, can be immensely disabling.[17,19–22]

Although most trials for alcohol dependence treatment do not explicitly seek to exclude individuals with comorbid independent mood and anxiety disorders,[12] widely used eligibility criteria may disproportionately impact these patients. Because of the high prevalence of independent mood and anxiety disorders in alcohol-dependent individuals and the impact of these comorbidities on alcohol dependence treatment outcomes,[10] it would be unfortunate if RCTs produced an evidence base that excluded them. Therefore, examining the prevalence of individuals with independent mood and anxiety disorders enrolled in clinical trials of alcohol dependence treatment is required and may help guide eligibility criteria operationalization for future clinical trials in alcohol dependence.

The aim of the present study was to estimate the proportion of alcohol-dependent individuals with independent mood and anxiety disorders that would have been eligible in alcohol treatment trials under typical eligibility criteria. We used a data set in which Grant and colleagues[17] had already determined the prevalence of *DSM-IV* mood and anxiety disorders among individuals with a current diagnosis of alcohol dependence: NESARC, a large (n = 43,093), nationally representative sample of the US adult population. We applied a standard set of exclusion criteria commonly used in clinical trials for alcohol dependence, using operationalizations previously described by Blanco and colleagues.[8] We then examined the proportion of alcohol-dependent individuals with and without independent mood and anxiety disorders that would have been eligible if the traditional clinical trial eligibility criteria were applied to these samples. Because individuals who seek treatment for a disorder may differ from those who do not,[1,3,6,8] we applied the eligibility criteria first to all participants with a current diagnosis of alcohol dependence and then to the subsample of participants seeking alcohol treatment. We hypothesized that alcohol-dependent individuals with a co-occurring independent mood or anxiety disorder would be disproportionately excluded in typical clinical trials of alcohol dependence treatment.

Clinical Points

- Over one third of the alcohol-dependent general population had a co-occurring independent mood or anxiety disorder, and more than 60% of these individuals would be ineligible for an alcohol dependence treatment trial under typical eligibility criteria.
- Independent mood and anxiety disorders were prevalent in the alcohol-dependent population but not in clinical trial research samples since almost every individual who had sought alcohol treatment would have been ineligible.
- For alcohol dependence trials to adequately inform clinical practice, the enrollment of patients with co-occurring mood or anxiety disorders must be increased through trials tailored to this population, a general relaxation of overly stringent eligibility criteria, or both.

METHOD

NESARC Sample

Data were drawn from the 2001–2002 NESARC, a nationally representative survey of the population of the United States conducted by the US Census Bureau under the direction of the National Institute on Alcohol Abuse and Alcoholism and described in detail elsewhere.[23] The target population included the civilian noninstitutionalized population, aged 18 years and older, residing in the United States. Face-to-face personal interviews were conducted with 43,093 respondents. The overall survey response rate was 81%. Black and Hispanic individuals and young adults (aged 18–24 years) were oversampled. Data were weighted at the individual and household levels in order to adjust for oversampling and nonresponse on demographic variables and be representative of the US civilian population based on the 2000 census. The research protocol, including written informed consent procedures, received full ethical review and approval from the US Census Bureau and the Office of Management and Budget.[24]

DSM-IV Diagnostic Interview

Lifetime and 12-month psychiatric diagnoses were made according to the *DSM-IV* criteria with the Alcohol Use Disorder and Associated Disabilities Interview Schedule—*DSM-IV* Version (AUDADIS-IV), a valid and reliable fully structured diagnostic interview designed for use by professional interviewers who are not clinicians.[17,23] The reliability of the AUDADIS-IV alcohol dependence diagnosis is well documented in clinical and general population samples,[25–27] with test-retest reliability ranging from good to excellent ($\kappa = 0.70–0.84$), and clinical reappraisal studies of *DSM-IV* alcohol use disorder diagnoses indicate good agreement between AUDADIS-IV and psychiatrist diagnoses ($\kappa = 0.60–0.76$).[27–29] The test-retest reliability[25,30] of the AUDADIS-IV diagnosis of major depression is good ($\kappa = 0.64–0.67$), and a clinical reappraisal study[28] of major depression indicated good agreement between AUDADIS-IV and psychiatrist diagnoses ($\kappa = 0.64–0.68$). The reliability of the AUDADIS-IV in assessing *DSM-IV* anxiety ($\kappa = 0.40–0.60$) and personality disorders ($\kappa = 0.40–0.67$) was fair to good,[25,28] and good to excellent for substance use disorders ($\kappa = 0.54–0.76$).[23,25–27]

Psychiatric Disorders Assessment

Psychiatric diagnoses, including alcohol dependence and mood and anxiety disorders, were made according to the *DSM-IV* criteria with the AUDADIS-IV. A diagnosis of alcohol dependence requires that a person meet at least 3 of the 7 dependence criteria. Because the *DSM-IV* considers alcohol dependence a syndrome, symptoms comprising 3 or more dependence criteria have to cluster within any 12-month period. The withdrawal criterion of the alcohol dependence diagnosis was measured as a syndrome, requiring at least 2 positive symptoms of withdrawal as defined in the *DSM-IV*, or 1 positive symptom of withdrawal relief/avoidance (ie, taking a drink or medicine or drug to avoid

or get over bad aftereffects of drinking). A person who meets criteria for both abuse and dependence is classified in the dependence category.

Psychiatric disorder diagnoses were primary (or "independent," ie, general medical condition or substance-induced mood disorders were ruled out). Disorders were classified as independent if (1) the respondent abstained from alcohol and drug use in the past 12 months or (2) the episode(s) did not occur in the context of alcohol or drug intoxication or withdrawal or (3) the episode(s) occurred before alcohol or drug intoxication or withdrawal or (4) the episode(s) began after alcohol or drug intoxication or withdrawal, but persisted for more than 1 month after the cessation of alcohol or drug intoxication or withdrawal.

Among participants with alcohol dependence during the year preceding the interview, the timeframe used by the AUDADIS-IV when assessing the presence of "current" symptoms, we distinguished those with a current diagnosis of major mood disorder (ie, major depressive episode, dysthymia, hypomania, and mania) or anxiety disorder (ie, panic disorder with and without agoraphobia, social anxiety disorder, specific phobia, and generalized anxiety disorder) from those without such a condition. Participants with current alcohol dependence who reported having sought help for alcohol dependence during the year preceding the interview were considered to be seeking treatment.

Clinical Trials Eligibility Criteria

We followed operationalizations of exclusion criteria with NESARC data described by Blanco and colleagues[8] and using traditional eligibility criteria summarized by Monahan and Finney[31] and formalized by Humphreys and colleagues[7] because they constitute the most representative summary of exclusion criteria used in treatment outcome studies for alcohol dependence to date. This summary gathered information from 701 alcohol treatment outcome studies and identified the most frequently used set of criteria in clinical trials of treatments for alcohol dependence.[31] These criteria are presented in Tables 1 and 2.

The percentages of individuals excluded by criteria 1 to 11 were estimated from data collected by the AUDADIS-IV, as described in detail elsewhere.[8] Information to approximate neurocognitive problems and residential stability was not available in the NESARC.

Statistical Analysis

Criteria for AUDADIS-IV diagnosis of alcohol dependence and mood and anxiety disorders were applied to the NESARC data for the analyses. Among survey participants with a 12-month *DSM-IV* diagnosis of alcohol dependence, we first determined the percentage (and 95% confidence interval) of those with a current diagnosis of independent mood or anxiety disorder who would have been eligible in clinical trials for alcohol dependence by individually applying each exclusion criterion. Because individuals might have been excluded by more than 1 criterion, we also calculated the overall percentage of subjects who would have been excluded by the simultaneous application of all criteria. Among survey participants with a current *DSM-IV* diagnosis of alcohol dependence (N = 1,484), we conducted these analyses for all participants with and without independent mood or anxiety disorders. As an internal control of our approach, the same criteria were applied to the subsample of individuals seeking treatment (n = 185) to examine potential differences in eligibility between treatment-seeking and non–treatment-seeking individuals. We then estimated the proportion of individuals with any independent mood or any anxiety disorder who would have been eligible in clinical trials for alcohol dependence with typical eligibility criteria.

Because of the weighting and clustering used in the NESARC design, all statistical analyses were performed using the Taylor series linearization method, a design-based method implemented using SUDAAN, version 10 (RTI International, Research Triangle Park, North Carolina). Significance tests of sets of coefficients were performed using Wald χ^2 tests based on design-corrected coefficient variance-covariance matrices. Due to the cross-sectional nature of the study, odds ratios were used as measures of association without implying any causal association.[32] Statistical significance was evaluated using a 2-sided design with α set at 0.05.

RESULTS

Participants with either independent mood or anxiety disorder represented 39.22% (SE = 1.67, n = 585) of the full sample and 52.59% (SE = 4.42, n = 96) of the treatment-seeking subsample, respectively, while the percentages of those with both independent mood and anxiety disorders were, respectively, 11.77% (SE = 1.06, n = 169) in the full sample and 25.09% (SE = 4.01, n = 39) in the treatment-seeking subsample.

Among participants with a current diagnosis of alcohol dependence, the proportion of individuals that would have been excluded by at least 1 of the 11 traditional and available eligibility criteria in clinical trials for alcohol dependence was 64.27% (SE = 2.98) in participants with a current mood disorder and 63.83% (SE = 3.60) in those with a current anxiety disorder (Table 1).

In the treatment-seeking subsample, almost every alcohol-dependent patient with an independent mood disorder (98.35%, SE = 1.17) and almost every alcohol-dependent patient with an anxiety disorder (97.43%, SE = 2.54) was prevented from trial enrollment by eligibility criteria (Table 2). The criteria leading to the highest exclusion rate were past-year illicit drug abuse or dependence, lack of motivation, and significant medical conditions for the full sample of individuals with a current diagnosis of any mood disorder or any anxiety disorder. Having a lack of motivation, a past-year illicit drug abuse or dependence, significant medical conditions, or a concurrent alcohol treatment resulted in the highest exclusion rate in the treatment-seeking subsample of individuals with any mood or any anxiety disorder.

In the full sample, the criteria that would exclude disproportionately subjects having a current diagnosis of any mood disorder were past-year psychotic disorder, distance

Table 1. Estimated Percentages[a] of Adults With Current Independent Mood and Anxiety Disorder in NESARC Who Would Have Been Excluded From Typical Clinical Trials of Treatments for Alcohol Dependence (N=1,484) by Traditional Efficacy Eligibility Criteria

Variable	Either Independent Mood or Anxiety Disorder (n = 585)	Both Independent Mood and Anxiety Disorders (n = 169)	Any Independent Mood Disorder (n = 430)	Any Independent Anxiety Disorder (n = 324)	Independent Mood Disorder Subgroup				Independent Anxiety Disorder Subgroup			
					Major Depressive Episode (n = 313)	Dysthymia (n = 74)	Mania (n = 119)	Hypomania (n = 75)	Panic Disorder (n = 97)	Social Anxiety Disorder (n = 88)	Specific Phobia (n = 185)	Generalized Anxiety Disorder (n = 87)
Traditional efficacy eligibility criteria (past 12 mo)[b]												
Psychotic disorder	4.38 (1.24)	11.18 (3.67)	5.89 (1.72)	6.01 (1.94)	6.91 (2.19)	13.96 (5.43)	8.10 (2.99)	1.93 (1.66)	9.17 (3.35)	4.22 (3.28)	6.17 (2.72)	5.54 (3.51)
Concurrent alcohol treatment	7.27 (1.26)	12.96 (3.12)	8.74 (1.60)	8.39 (1.87)	9.05 (2.11)	16.99 (5.79)	10.81 (3.46)	4.57 (2.46)	8.90 (3.60)	7.68 (2.94)	8.28 (2.46)	13.92 (4.84)
Medical conditions	22.99 (2.18)	34.91 (4.51)	25.33 (2.49)	26.23 (3.22)	25.38 (3.04)	32.86 (6.84)	30.71 (5.32)	25.53 (5.91)	30.15 (4.75)	30.20 (6.61)	23.07 (4.29)	37.52 (6.91)
Noncompliance/lack of motivation	26.60 (2.38)	28.56 (4.16)	26.78 (2.74)	27.37 (3.17)	29.02 (3.35)	52.50 (6.96)	26.50 (4.60)	10.71 (4.05)	33.04 (5.51)	34.96 (6.53)	23.58 (3.85)	37.84 (6.04)
Demographic (age > 65 y)	1.10 (0.42)	1.68 (1.00)	1.32 (0.54)	1.12 (0.58)	1.26 (0.62)	0.85 (0.85)	0.86 (0.85)	0.00	0.00	1.06 (1.06)	1.43 (0.85)	0.00
Illicit drug abuse or dependence	29.15 (2.76)	36.17 (4.87)	32.26 (3.34)	29.01 (3.36)	30.67 (3.68)	45.84 (7.77)	39.29 (5.75)	27.60 (6.45)	38.30 (5.25)	26.03 (4.98)	30.93 (4.44)	34.27 (6.53)
Social instability	6.54 (1.27)	12.56 (3.29)	7.31 (1.58)	8.67 (1.96)	7.93 (1.99)	16.53 (4.56)	9.61 (2.93)	0.38 (0.38)	8.54 (2.90)	7.73 (2.90)	10.19 (2.93)	10.93 (3.62)
Distance from treatment	2.46 (0.72)	3.53 (1.43)	2.74 (0.89)	2.66 (0.94)	3.48 (1.17)	7.66 (3.51)	3.08 (1.84)	0.00	4.65 (2.35)	4.27 (2.10)	1.39 (0.86)	6.23 (2.79)
Education/literacy	0.41 (0.22)	0.70 (0.63)	0.47 (0.30)	0.49 (0.35)	0.40 (0.36)	0.33 (0.33)	0.41 (0.40)	0.00	0.00	0.13 (0.13)	0.60 (0.54)	0.55 (0.55)
Legal problems	17.41 (2.09)	17.41 (3.61)	19.26 (2.51)	15.23 (2.48)	16.52 (2.73)	38.74 (7.88)	35.49 (5.05)	4.45 (2.50)	17.89 (4.04)	13.98 (4.04)	13.72 (3.12)	24.65 (5.77)
Financial situation	9.20 (1.56)	11.47 (3.02)	8.79 (1.64)	10.82 (2.34)	9.45 (2.04)	23.28 (6.81)	11.63 (3.23)	3.68 (2.31)	12.82 (3.81)	17.25 (5.96)	8.67 (2.86)	18.81 (4.98)
Neurocognitive problems	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Residential instability	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Excluded by at least 1 criterion	62.29 (2.68)	69.98 (4.60)	64.27 (2.98)	63.83 (3.60)	63.71 (3.63)	87.30 (3.96)	71.12 (5.18)	51.78 (6.61)	72.65 (5.17)	67.87 (5.97)	60.79 (4.66)	71.05 (5.86)
Eligible participants	37.71 (2.68)	30.02 (4.60)	35.73 (2.98)	36.17 (3.60)	36.29 (3.63)	12.70 (3.96)	28.88 (5.18)	48.22 (6.61)	27.35 (5.17)	32.13 (5.97)	39.21 (4.66)	28.95 (5.86)

[a]Percentages are weighted values. All values in table shown as % (SE).
[b]Derived from Humphreys and colleagues[7] (method described in their article).
Abbreviations: NA = information not available in NESARC, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

from treatment, illicit drug abuse or dependence, and financial situation, whereas these criteria were past-year psychotic disorder, distance from treatment, financial situation, and social instability among those with a current diagnosis of any anxiety disorder (Table 3). In the treatment-seeking subsample, having a past-year psychotic disorder and a significant medical condition were the criteria that significantly excluded subjects with a current diagnosis of any mood disorder, whereas past-year psychotic disorder and financial situation were those excluding participants with a current diagnosis of any anxiety disorder compared to those without such a condition.

In the full sample of patients with a current diagnosis of alcohol dependence, prevalences of current independent mood and anxiety disorders in participants that would have been eligible in typical clinical trials for alcohol dependence were significantly lower compared to the general population (from 27% for major depressive episode to 75% for dysthymia), except for hypomania, social anxiety disorder, and specific phobia (Table 4). Given that almost every single patient was excluded in the treatment-seeking sample, no comparable statistical test could be done, but, obviously, any population that is excluded nearly 100% of the time will be underrepresented in clinical research.

DISCUSSION

Building on a prior NESARC study by Grant and colleagues,[17] the present study estimated the proportion of adults with alcohol dependence and comorbid independent mood or anxiety disorders that would have been included under typical eligibility criteria in clinical trials of alcohol dependence treatment. We found that eligible individuals have substantially lower rates of mood (ie, major depression, mania, and dysthymia) and anxiety disorders (ie, panic disorder and generalized anxiety disorder).

Consistent with prior research,[7,8,10–12] including a recent study examining generalizability of clinical trial results for current alcohol dependence using the same database,[8] findings indicate that eligibility criteria in clinical trials tend to exclude a majority of individuals with alcohol dependence, supporting the view that clinical trials suffer from impaired external validity since their results may not be readily generalizable either to community samples or to treatment-seeking populations.

Restrictive eligibility criteria used by RCTs at the cost of diminished external validity can sometimes be justified.[1] However, beyond impaired external validity, we found that applying some traditional eligibility criteria (eg, past-year psychotic disorder, distance from treatment, illicit drug abuse or

Table 2. Estimated Percentages[a] of Adults With a Current Alcohol Dependence and Seeking Treatment for Alcohol Dependence in NESARC (N=185) Who Would Have Been Excluded From Typical Clinical Trials of Treatments for Alcohol Dependence by Traditional Efficacy Eligibility Criteria

					Independent Mood Disorder Subgroup				Independent Anxiety Disorder Subgroup			
Variable	Either Independent Mood or Anxiety Disorder (n = 96)	Both Independent Mood and Anxiety Disorders (n = 39)	Any Independent Mood Disorder (n = 78)	Any Independent Anxiety Disorder (n = 57)	Major Depressive Episode (n = 60)	Dysthymia (n = 19)	Mania (n = 23)	Hypomania (n = 8)	Panic Disorder (n = 23)	Social Anxiety Disorder (n = 15)	Specific Phobia (n = 30)	Generalized Anxiety Disorder (n = 19)
Traditional efficacy eligibility criteria (past 12 mo)[b]												
Psychotic disorder	18.69 (5.14)	29.16 (9.19)	21.85 (6.17)	22.33 (6.87)	23.47 (7.44)	38.00 (14.47)	29.88 (11.14)	21.63 (16.97)	29.71 (10.12)	24.79 (17.01)	23.46 (9.37)	20.17 (12.71)
Concurrent alcohol treatment	44.70 (6.05)	50.16 (9.36)	47.91 (6.94)	44.81 (7.61)	48.09 (8.27)	61.73 (13.09)	50.55 (11.91)	51.21 (18.38)	35.75 (11.82)	48.73 (15.71)	50.19 (10.19)	56.94 (13.37)
Medical conditions	41.81 (5.51)	57.40 (9.23)	49.66 (6.40)	43.62 (7.38)	49.59 (7.96)	64.03 (12.87)	69.14 (10.24)	51.13 (18.28)	48.98 (11.37)	47.10 (15.62)	54.01 (10.05)	50.86 (13.74)
Noncompliance/lack of motivation	54.34 (5.83)	65.24 (9.09)	58.72 (6.40)	56.88 (7.59)	61.08 (7.35)	81.15 (8.75)	41.29 (11.73)	54.72 (17.89)	55.53 (12.23)	61.20 (16.59)	59.13 (9.99)	76.63 (10.61)
Demographic (age > 65 y)	1.31 (1.30)	2.75 (2.72)	1.66 (1.65)	1.90 (1.89)	2.17 (2.15)	0.00	0.00	0.00	0.00	0.00	3.66 (3.60)	0.00
Illicit drug abuse or dependence	43.03 (6.22)	43.58 (9.25)	45.40 (6.64)	40.69 (7.72)	41.84 (7.46)	64.56 (12.79)	46.70 (11.86)	38.32 (18.11)	54.07 (12.14)	46.71 (15.54)	48.40 (10.21)	45.41 (13.97)
Social instability	10.84 (3.02)	16.43 (5.58)	10.85 (3.35)	14.70 (4.46)	10.53 (3.81)	9.87 (5.83)	14.06 (6.92)	0.00	18.59 (7.33)	27.84 (12.59)	22.61 (7.76)	12.09 (6.24)
Distance from treatment	8.44 (3.19)	7.31 (4.00)	7.15 (3.10)	9.14 (4.04)	8.21 (3.88)	11.61 (8.34)	8.14 (5.91)	0.00	16.48 (8.32)	17.83 (10.90)	8.41 (5.09)	10.39 (7.61)
Education/literacy	0.73 (0.55)	0.00	0.31 (0.31)	0.72 (0.72)	0.00	1.21 (1.24)	0.00	0.00	0.00	0.00	0.00	2.26 (2.29)
Legal problems	37.62 (5.80)	32.77 (8.24)	42.81 (6.44)	28.32 (6.45)	35.70 (6.85)	48.55 (14.06)	56.91 (11.98)	32.49 (19.51)	42.28 (10.97)	33.75 (13.93)	19.30 (7.17)	48.35 (13.67)
Financial situation	24.29 (5.29)	27.65 (8.23)	24.38 (5.94)	26.51 (6.67)	22.81 (6.59)	46.21 (14.39)	17.98 (8.23)	35.11 (18.21)	28.49 (10.20)	40.00 (14.78)	32.08 (9.81)	47.01 (13.82)
Neurocognitive problems	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Residential instability	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Excluded by at least 1 criterion	96.93 (1.97)	100.00	98.35 (1.17)	97.43 (2.54)	97.85 (1.52)	100.00	100.00	100.00	100.00	100.00	95.06 (4.80)	100.00
Eligible participants	3.07 (1.97)	0.00	1.65 (1.17)	2.57 (2.54)	2.15 (1.52)	0.00	0.00	0.00	0.00	0.00	4.94 (4.80)	0.00

[a]Percentages are weighted values. All values in table shown as % (SE).
[b]Derived from Humphreys and colleagues[7] (method described in their article).
Abbreviations: NA = information not available in NESARC, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

dependence, financial situation, and social instability) may result in a selection bias, preferentially excluding participants with independent mood and anxiety disorders, particularly among participants likely to seek treatment.

Prior research establishes that alcohol-dependent individuals with independent mood or anxiety disorders have poorer outcomes than their counterparts in alcohol dependence relapse,[18] suicide risk,[17] and impairment.[17,19–22] In addition, Grant and colleagues[17] found that a substantial proportion of participants with alcohol dependence, particularly those seeking treatment, have a comorbid independent mood or anxiety disorder. With that in mind, excluding these individuals might be a disservice to clinical practice. Although most trials do not seek to exclude these participants by using this specific criterion, our results suggest that applying some traditional eligibility criteria may nonetheless result in excluding these participants in RCTs for alcohol dependence, particularly those seeking treatment.

While some of the exclusion criteria may have been implemented due to practical constraints the researcher could not control (eg, insufficient resources to follow up individuals who live too far from the treatment program), implementing others (or not) was within the researchers' control (eg, social instability). Those decisions could be questioned in cases in which the chosen criteria excluded a large proportion of patients and thereby negatively affected impact on external validity.

We would make some cautionary notes about our study. First, we followed a methodology for identifying and operationalizing exclusion criteria developed by Humphreys and colleagues[7] and previously applied to the NESARC sample by Blanco and colleagues.[8] Other conventions might have yielded different exclusion estimates. For example, the 12-month timeframe used by the AUDADIS-IV when assessing the presence of "current" symptoms could have led to an overestimation of the exclusion rate and may have biased the estimated proportion of participants with a current independent mood and anxiety disorder that would have been potentially eligible in RCTs for alcohol dependence. In addition, 2 of the exclusion criteria (ie, neurocognitive problems and residential instability) could not be operationalized using the NESARC and theoretically may have led to an underestimation of the proportion of participants excluded from clinical trials. However, the percentage of excluded participants was high and consistent with those observed in earlier research.[7,8,10–12]

Second, our approach focuses on the a priori eligibility of participants and was based on national epidemiologic data.[1] It provides no information on

Table 3. Comparisons of Exclusion Rates From Typical Clinical Trials of Treatments for Alcohol Dependence Between Individuals With and Without Any Independent Mood or Anxiety Disorder in NESARC, by Traditional Efficacy Eligibility Criteria[a]

	Full Sample (N = 1,484)		Treatment-Seeking Sample (n = 185)	
Variable	Any Independent Mood Disorder	Any Independent Anxiety Disorder	Any Independent Mood Disorder	Any Independent Anxiety Disorder
Traditional efficacy eligibility criteria (past 12 mo)[b]				
Psychotic disorder	**20.37 (7.57–54.80)*****	**11.14 (3.97–31.27)*****	**13.58 (3.44–53.58)*****	**8.22 (1.90–35.59)****
Concurrent alcohol treatment	**2.16 (1.31–3.56)****	**1.90 (1.08–3.36)***	1.20 (0.60–2.41)	0.97 (0.47–2.02)
Medical conditions	**2.22 (1.61–3.05)*****	**2.25 (1.51–3.36)*****	**2.88 (1.30–6.38)****	1.73 (0.80–3.73)
Noncompliance/lack of motivation	**1.83 (1.28–2.61)****	**1.84 (1.27–2.66)****	1.14 (0.56–2.33)	1.00 (0.45–2.22)
Demographic (age > 65 y)	1.61 (0.58–4.47)	1.23 (0.38–3.96)	…	…
Illicit drug abuse or dependence	**2.45 (1.66–3.59)*****	**1.84 (1.25–2.71)****	1.68 (0.87–3.24)	1.18 (0.54–2.57)
Social instability	**2.01 (1.16–3.50)***	**2.59 (1.42–4.71)****	1.87 (0.61–5.72)	…
Distance from treatment	**4.30 (1.55–11.99)****	**3.42 (1.23–9.56)***	…	…
Education/literacy	0.32 (0.09–1.15)	0.34 (0.07–1.66)	…	…
Legal problems	**2.15 (1.48–3.14)*****	1.35 (0.88–2.08)	1.90 (0.92–3.90)	0.65 (0.28–1.52)
Financial situation	**2.37 (1.35–4.17)****	**3.30 (1.79–6.08)*****	2.45 (0.91–6.58)	**2.78 (1.07–7.23)***
Neurocognitive problems	NA	NA	NA	NA
Residential instability	NA	NA	NA	NA
Excluded by at least 1 criterion	**2.20 (1.64–2.96)*****	**2.06 (1.46–2.90)*****	**5.50 (1.08–28.03)***	3.01 (0.35–25.79)

[a]Values shown as OR (95% CI). Odds ratios (ORs) were estimated through logistic regression ($df = 1$). OR values in bold are statistically significant ($P < .05$).
[b]Derived from Humphreys and colleagues[7] (method described in their article).
*$P < .05$. **$P < .01$. ***$P < .001$.
Abbreviations: NA = information not available in NESARC, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.
Symbol: … = not applicable.

Table 4. Comparisons of Proportions of Individuals With Any Independent Mood or Anxiety Disorder Who Would Have Been Eligible in Clinical Trials for Alcohol Dependence With Typical Eligibility Criteria With Those in the General Population[a]

	General Population, % (SE)		Eligible Population, % (SE)		
Mood and Anxiety Disorders	Full Sample (n = 1,484)	Treatment-Seeking Sample (n = 185)	Full Sample (n = 724)	Treatment-Seeking Sample (n = 12)	Eligible Population vs General Population, OR (CI)[b]
Either independent mood or anxiety disorder	39.22 (1.67)	52.59 (4.42)	29.75 (2.18)	28.72 (15.63)	**0.51 (0.41–0.63)*****
Both independent mood and anxiety disorders	11.77 (1.06)	25.09 (4.01)	7.11 (1.13)	0.00	**0.45 (0.32–0.63)*****
Any independent mood disorder	27.55 (1.53)	41.47 (4.34)	19.80 (1.62)	12.16 (8.56)	**0.49 (0.39–0.62)*****
Major depressive episode	20.48 (1.43)	31.78 (4.39)	14.95 (1.53)	12.16 (8.56)	**0.56 (0.43–0.72)*****
Dysthymia	4.63 (0.67)	10.52 (2.84)	1.18 (0.37)	0.00	**0.32 (0.17–0.59)*****
Mania	7.63 (0.83)	13.46 (2.82)	4.43 (0.86)	0.00	**0.34 (0.22–0.52)*****
Hypomania	4.99 (0.62)	3.89 (1.69)	4.84 (0.83)	0.00	0.93 (0.58–1.47)
Any independent anxiety disorder	23.45 (1.42)	36.20 (4.27)	17.06 (1.85)	16.55 (14.67)	**0.74 (0.59–0.93)****
Panic disorder	6.54 (0.77)	13.44 (3.10)	3.60 (0.78)	0.00	**0.51 (0.33–0.80)****
Social anxiety disorder	6.25 (0.85)	8.12 (2.47)	4.04 (0.81)	0.00	0.66 (0.43–1.01)
Specific phobia	13.84 (1.15)	18.83 (3.26)	10.92 (1.56)	16.55 (14.67)	0.86 (0.65–1.14)
Generalized anxiety disorder	5.69 (0.71)	11.47 (2.96)	3.31 (0.77)	0.00	**0.55 (0.35–0.87)***

[a]Percentages are weighted values. ORs were estimated through logistic regression ($df = 1$). OR values in bold are statistically significant ($P < .05$).
[b]Comparisons were applicable only for the full sample.
*$P < .05$. **$P < .01$. ***$P < .001$.
Symbol: … = not applicable.

individuals who actually enter those studies. In fact, a substantial proportion of eligible individuals may be unwilling to participate.[33] Furthermore, the likelihood of entering a trial may be influenced by several factors, including anxiety, extroversion, and performance measures.[34]

Third, mood and anxiety disorders were independent in our analyses according to *DSM-IV* criteria. However, intoxication and withdrawal symptoms often resemble symptoms of mood and anxiety disorders, which possibly could have impeded the diagnosis of "independent" comorbidity.

Last, we used traditional eligibility criteria summarized by Monahan and Finney[31] and formalized by Humphreys and colleagues[7] because they constitute the most representative summary of exclusion criteria used in treatment outcome studies for alcohol dependence to date. However, these references are 8 years old, and the alcohol treatment research field has since increased attention to and reporting of exclusion criteria.[35] It would therefore be worthwhile to attempt to replicate the present results using data on exclusion criteria from alcohol treatment studies conducted in recent years.

Despite these concerns, the present study suggests that the current design of clinical trials for alcohol dependence suffers from impaired external validity, particularly excluding individuals with a comorbid independent mood or anxiety disorder. The use of some exclusion criteria, including past-year psychotic disorder, distance from treatment, illicit drug abuse or dependence, financial situation, and social instability, may play a substantial role in this selection bias. Until funding and regulatory agencies emphasize the importance of more inclusive eligibility criteria,[36,37] future clinical trials

for alcohol dependence studies would benefit from examining alcohol dependence treatment efficacy in this specific population by doing studies tailored to this population and/or by reducing exclusion criteria and raising sample sizes sufficiently so that any resulting heterogeneity in treatment response is overcome.[38]

Author affiliations: Assistance Publique-Hôpitaux de Paris (AP-HP), Corentin-Celton Hospital, Department of Psychiatry, 92130 Issy-les-Moulineaux and Paris Descartes University, PRES Sorbonne Paris Cité (Drs Hoertel, Seigneurie, and Limosin); Center of Psychiatry and Neuroscience, Sainte-Anne Hospital, INSERM UMR 894; Paris Descartes University, PRES Sorbonne Paris Cité (Drs Hoertel, Gorwood, and Limosin); National Institute for Health and Medical Research (INSERM), Unit UMR-S0669, and Paris-Sud and Paris Descartes Universities (Dr Falissard), Paris, France; Veterans Affairs and Stanford University Medical Centers, Palo Alto, California (Dr Humphreys); and Sainte-Anne Hospital, Clinique des Maladies Mentales et de l'Encéphale (CMME), Paris Descartes University, PRES Sorbonne Paris Cité, Paris, France (Dr Gorwood).

Potential conflicts of interest: **Dr Falissard** acknowledges consultancies (Eli Lilly, Novartis, Roche, Pfizer) and honoraria (Bristol-Myers Squibb, GlaxoSmithKline, Servier, Astellas, Genzyme, Sanofi). **Dr Gorwood** acknowledges consultancies (Eli Lilly, Servier, Janssen-Cilag), grant/research support (Eli Lilly, Servier), and speakers or advisory board participation (AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Servier). **Dr Limosin** acknowledges speakers or advisory board participation (Janssen, Lundbeck, Roche, Servier). **Drs Hoertel, Humphreys,** and **Seigneurie** report no conflicts of interest.

Funding/support: Dr Humphreys was supported by a Research Career Scientist award from the Department of Veterans Affairs. Drs Falissard, Gorwood, Limosin, and Hoertel report no sources of funding.

Acknowledgment: The authors thank the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for making their dataset publicly available.

Additional information: Original data set for the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is available from the National Institute on Alcohol Abuse and Alcoholism (http://www.niaaa.nih.gov).

REFERENCES

1. Blanco C, Olfson M, Goodwin RD, et al. Generalizability of clinical trial results for major depression to community samples: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69(8):1276–1280.
2. Hoertel N, Le Strat Y, De Maricourt P, et al. Are subjects in treatment trials of panic disorder representative of patients in routine clinical practice? results from a national sample. *J Affect Disord*. 2013;146(3):383–389.
3. Hoertel N, Le Strat Y, Lavaud P, et al. Generalizability of clinical trial results for bipolar disorder to community samples: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(3):265–270.
4. Hoertel N, Le Strat Y, Limosin F, et al. Prevalence of subthreshold hypomania and impact on internal validity of RCTs for major depressive disorder: results from a national epidemiological sample. *PLoS ONE*. 2013;8(2):e55448.
5. Dzewaltowski DA, Estabrooks PA, Klesges LM, et al. Behavior change intervention research in community settings: how generalizable are the results? *Health Promot Int*. 2004;19(2):235–245.
6. Hoertel N, Le Strat Y, Angst J, et al. Subthreshold bipolar disorder in a US national representative sample: prevalence, correlates and perspectives for psychiatric nosography. *J Affect Disord*. 2013;146(3):338–347.
7. Humphreys K, Weingardt KR, Horst D, et al. Prevalence and predictors of research participant eligibility criteria in alcohol treatment outcome studies, 1970–98. *Addiction*. 2005;100(9):1249–1257.
8. Blanco C, Olfson M, Okuda M, et al. Generalizability of clinical trials for alcohol dependence to community samples. *Drug Alcohol Depend*. 2008;98(1–2):123–128.
9. Van Spall HG, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA*. 2007;297(11):1233–1240.
10. Humphreys K, Harris AH, Weingardt KR. Subject eligibility criteria can substantially influence the results of alcohol-treatment outcome research. *J Stud Alcohol Drugs*. 2008;69(5):757–764.
11. Humphreys K, Weingardt KR, Harris AH. Influence of subject eligibility criteria on compliance with National Institutes of Health guidelines for inclusion of women, minorities, and children in treatment research. *Alcohol Clin Exp Res*. 2007;31(6):988–995.
12. Humphreys K, Weisner C. Use of exclusion criteria in selecting research subjects and its effect on the generalizability of alcohol treatment outcome studies. *Am J Psychiatry*. 2000;157(4):588–594.
13. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. *Am J Psychiatry*. 2005;162(5):836–846.
14. Haver B. Comorbid psychiatric disorders predict and influence treatment outcome in female alcoholics. *Eur Addict Res*. 2003;9(1):39–44.
15. McLellan AT, Luborsky L, Woody GE, et al. Predicting response to alcohol and drug abuse treatments: role of psychiatric severity. *Arch Gen Psychiatry*. 1983;40(6):620–625.
16. Stoffelmayr BE, Benishek LA, Humphreys K, et al. Substance abuse prognosis with an additional psychiatric diagnosis: understanding the relationship. *J Psychoactive Drugs*. 1989;21(2):145–152.
17. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61(8):807–816.
18. Hasin D, Liu X, Nunes E, et al. Effects of major depression on remission and relapse of substance dependence. *Arch Gen Psychiatry*. 2002;59(4):375–380.
19. Roy-Byrne PP, Stang P, Wittchen HU, et al. Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. *Br J Psychiatry*. 2000;176(3):229–235.
20. Goetzel RZ, Hawkins K, Ozminkowski RJ, et al. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large US employers in 1999. *J Occup Environ Med*. 2003;45(1):5–14.
21. Sanderson K, Andrews G. Prevalence and severity of mental health-related disability and relationship to diagnosis. *Psychiatr Serv*. 2002;53(1):80–86.
22. Stewart WF, Ricci JA, Chee E, et al. Cost of lost productive work time among US workers with depression. *JAMA*. 2003;289(23):3135–3144.
23. Grant BF, Harford TC, Dawson DA, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability of alcohol and drug modules in a general population sample. *Drug Alcohol Depend*. 1995;39(1):37–44.
24. Grant BF, Dawson DA, Stinson FS, et al. The 12-month prevalence and trends in *DSM-IV* alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. *Drug Alcohol Depend*. 2004;74(3):223–234.
25. Grant BF, Dawson DA, Stinson FS, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend*. 2003;71(1):7–16.
26. Chatterji S, Saunders JB, Vrasti R, et al. Reliability of the alcohol and drug modules of the Alcohol Use Disorder and Associated Disabilities Interview Schedule-Alcohol/Drug-Revised (AUDADIS-ADR): an international comparison. *Drug Alcohol Depend*. 1997;47(3):171–185.
27. Hasin D, Carpenter KM, McCloud S, et al. The Alcohol Use Disorder and Associated Disabilities Interview Ichedule (AUDADIS): reliability of alcohol and drug modules in a clinical sample. *Drug Alcohol Depend*. 1997;44(2–3):133–141.
28. Canino G, Bravo M, Ramírez R, et al. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J Stud Alcohol*. 1999;60(6):790–799.
29. Cottler LB, Grant BF, Blaine J, et al. Concordance of *DSM-IV* alcohol and drug use disorder criteria and diagnoses as measured by AUDADIS-ADR, CIDI and SCAN. *Drug Alcohol Depend*. 1997;47(3):195–205.
30. Hasin DS, Goodwin RD, Stinson FS, et al. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*. 2005;62(10):1097–1106.
31. Monahan SC, Finney JW. Explaining abstinence rates following treatment for alcohol abuse: a quantitative synthesis of patient, research design and treatment effects. *Addiction*. 1996;91(6):787–805.
32. Le Strat Y, Hoertel N. Correlation is no causation: gymnasium proliferation and the risk of obesity. *Addiction*. 2011;106(10):1871–1872.
33. Melberg HO, Humphreys K. Ineligibility and refusal to participate in randomised trials of treatments for drug dependence. *Drug Alcohol Rev Mar*. 2010;29(2):193–201.
34. Mavissakalian MR, Guo S. Predictors of entering a long-term drug treatment study of panic disorder. *Compr Psychiatry*. 2002;43(2):88–94.
35. Humphreys K, Maisel NC, Blodgett JC, et al. Extent and reporting of patient nonenrollment in influential randomized clinical trials, 2002 to 2010. *JAMA Intern Med*. 2013;173(11):1029–1031.
36. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365(9453):82–93.
37. Hoertel N, Le Strat Y, Blanco C, et al. Generalizability of clinical trial results for generalized anxiety disorder to community samples. *Depress Anxiety*. 2012;29(7):614–620.
38. Geddes JR. Large simple trials in psychiatry: providing reliable answers to important clinical questions. *Epidemiol Psichiatr Soc*. 2005;14(3):122–126.