Title

A Meta-Regression of Trial Features Predicting the Effects of Alcohol Use Disorder Pharmacotherapies on Drinking Outcomes in Randomized Clinical Trials: A Secondary Data Analysis.

Journal

Alcohol and alcoholism (Oxford, Oxfordshire), 57(5)

ISSN

0735-0414

Authors

Grodin, Erica N
Donato, Suzanna
Du, Han
et al.

Publication Date

2022-09-01

DOI

10.1093/alcalc/agac004

Peer reviewed

Alcohol and Alcoholism, 2022, **57**(5), 589–594
https://doi.org/10.1093/alcalc/agac004
Advance access publication date 1 March 2022
Article

A Meta-Regression of Trial Features Predicting the Effects of Alcohol Use Disorder Pharmacotherapies on Drinking Outcomes in Randomized Clinical Trials: A Secondary Data Analysis

Erica N. Grodin[1], Suzanna Donato[1], Han Du[1], ReJoyce Green[1], Spencer Bujarski[1], and Lara A. Ray[1,2,*]

[1]Department of Psychology, University of California, 502 Portola Plaza, Los Angeles, California 90095 USA
[2]Department of Psychiatry and Biobehavioral Sciences. University of California, 757 Westwood Plaza #4, Los Angeles, CA 90095 USA
*Corresponding author: Psychology Department, Shirley M. Hatos Term Chair in Clinical Neuropharmacology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA. Tel.: +1-310-794-5383; Fax: +1-310-206-5895; Email: lararay@psych.ucla.edu

Abstract

Aims: To test whether two critical design features, inclusion criteria of required pre-trial abstinence and pre-trial alcohol use disorder (AUD) diagnosis, predict the likelihood of detecting treatment effects in AUD pharmacotherapy trials.
Methods: This secondary data analysis used data collected from a literature review to identify randomized controlled pharmacotherapy trials for AUD. Treatment outcomes were selected into abstinence and no heavy drinking. Target effect sizes were calculated for each outcome and a meta-regression was conducted to test the effects of required pre-trial abstinence, required pre-trial AUD diagnosis, and their interaction on effect sizes. A sub-analysis was conducted on trials, which included FDA-approved medications for AUD.
Results: In total, 118 studies testing 19 medications representing 21,032 treated participants were included in the meta-regression analysis. There was no significant effect of either predictor on abstinence or no heavy drinking outcomes in the full analysis or in the sub-study of FDA-approved medications.
Conclusion: By examining these design features in a quantitative, rather than qualitative, fashion the present study advances the literature and shows that requiring AUD diagnosis or requiring pre-trial abstinence do not impact the likelihood of a significant medication effect in the trial.

INTRODUCTION

Medication development is a costly and time-consuming endeavor. It is estimated that central nervous system (CNS) compounds (e.g. those needed for the treatment of psychiatric disorders, including alcohol use disorder (AUD)) take approximately 18 years to get from discovery to market and cost more than $1.8 billion (Kaitin and Milne, 2011; Litten *et al*., 2016). The high cost and slow rate of drug development are caused, in part, by the high failure rate of these medications. Less than 8% of new CNS compounds entering Phase I (i.e. safety and dosage testing in healthy volunteers) will be approved for clinical use (Kaitin and Milne, 2011). To date, only three medications have received FDA approval for the treatment of AUD: disulfiram, acamprosate and naltrexone. While acamprosate and naltrexone are shown to have moderate efficacy (Jonas *et al*., 2014), the heterogeneous nature of AUD necessitates a broader set of treatment options. Thus, medication development is a top research priority (Litten *et al*., 2012; Litten *et al*., 2016; Ray *et al*., 2018), with various resources being allocated to the advancement of novel treatment options. Initiatives such as the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) Clinical Investigations Group (NCIG) have been created to streamline the medication development process. The goal of NCIG is to identify and test novel compounds to treat AUD, while also adapting current off-label medications. To best achieve this goal, we must maximize efficiency across all stages of clinical testing of AUD pharmacotherapies.

The primary purpose for conducting clinical trials of AUD pharmacotherapies is to identify efficacious treatments, with a secondary purpose of determining which treatments are most efficacious for which patients. While there are multiple steps in the drug development process, conducting clinical trials is perhaps the most critical. Of the $1.8 billion spent developing each compound, nearly half of that cost is spent in conducting clinical trials. Moreover, only 46% of new compounds succeed in the pivotal (i.e. Phase III) clinical trials. To maximize the efficiency of these trials, researchers established standardized practices for clinical trials. Examples of such efforts include creating the Consolidated Standards of Reporting Trials (CONSORT) statement (Begg *et al*., 1996), forming the Alcohol Clinical Trials Initiative (ACTIVE) workgroup (Anton *et al*., 2012), and prioritizing research to optimize methodological practices (Litten *et al*., 2012). In a landmark study, Miller and Wilbourne (2002) reviewed over 361 controlled trials and found that methodological quality was a significant predictor of whether a trial reported a significant treatment effect. These findings highlighted the significance of strong methodological quality and standardized practices in clinical trials. More recently, Witkiewitz *et al*. (2015a) provided a narrative review of published clinical trials for AUD to offer recommendations for best reporting practices,

Received: September 3, 2021. **Revised:** January 11, 2022. **Editorial decision:** January 16, 2022. **Accepted:** January 16, 2022

including the consistent use of state-of-the-art design features and analytic methods. With the benefit of these important qualitative reviews, the next step in refining clinical trials methodology is to take a data-driven approach to evaluating methodological features of AUD clinical trials.

The methodology applied to AUD pharmacotherapy trials is complex, consisting of several major components such as study design, data management, population selection, recruitment, adherence, retention, outcome measures, goals of pharmacological treatment (i.e. achieving and maintaining abstinence or harm reduction) and safety. Appropriate trial design is crucial to the execution of clinical trials as empirical evidence has demonstrated that inadequate design is associated with biased estimates of treatment effects (Schulz *et al*., 1995). To reduce the risk of bias, as well as streamline the development process, preliminary research examined the extent to which specific design features for clinical trials impacted the ability to detect an effect. Early studies on eligibility criteria found that exclusion criteria (e.g. psychiatric problems, medical conditions, comorbid drug use) may increase bias in outcome estimates and hinder the generalizability of results (Humphreys and Weisner, 2000; Humphreys *et al*., 2008). Other design features such as outcome measures (Falk *et al*., 2010; Falk *et al*., 2014), multi-site versus single-site trials (Feinn and Kranzler, 2005), missing data approaches (Witkiewitz *et al*., 2014; Hallgren *et al*., 2016) and participant treatment-seeking status (Ray *et al*., 2017; Rohn *et al*., 2017) have been investigated for their impact on the medication effect size. Together, this foundational research established that various methodological factors can impact the results of clinical trials. Given these findings, more research needs to be conducted to elucidate the impact of other customary design features.

The present study uses a meta-regression approach to test two critical design features in AUD clinical trials, namely (a) requirement of pre-trial alcohol abstinence and (b) requirement of pre-trial AUD diagnosis. These two design features address key and unanswered questions in clinical trial design for AUD (Anton *et al*., 2012). Specifically, this study will test whether two critical design features (i.e. inclusion criteria of pre-trial abstinence and pre-trial AUD diagnosis) predict the likelihood of detecting treatment effects (i.e. abstinence and no heavy drinking). A literature review was conducted to identify pharmacotherapies tested for AUD using both behavioral pharmacotherapy and RCT methodologies (Ray *et al*., 2021). The study sample is comprised of clinical trials for both FDA-approved and non–FDA-approved medications ($k = 118$). Of note, no studies evaluating disulfiram were included in the current study as no studies investigated disulfiram using behavioral pharmacotherapy approaches. We hypothesize that the two selected design features (i.e. predictors) will influence treatment response, such that clinical trials requiring pre-trial abstinence and pre-trial AUD diagnosis will show higher treatment effects than those without the requirements. We also conducted a sub-study of clinical trials with FDA-approved medications only ($k = 72$). We similarly hypothesize that the two predictors will influence treatment response in the same direction.

MATERIALS AND METHODS

Literature review

This was a secondary data analysis of a previously published meta-analysis examining the predictive relationship of human laboratory findings on clinical trial outcomes (Ray *et al*., 2021). Inclusion criteria for the RCT studies were (a) a randomized controlled trial, (b) single or double blinded, (c) placebo or active control condition, (d) primary endpoint of alcohol use, (e) ≥4 weeks of treatment, (f) ≥12 weeks of follow-up and (g) medication tested in behavioral pharmacotherapy trial. Full details of the algorithmic literature search can be found in (Ray *et al*., 2021). The literature search identified 2028 records, of which 132 were subjected to full-text review, resulting in 118 included in this analysis representing 19 medications.

Selection of outcomes and predictors

Two continuous outcomes were analyzed based on current Administration, FaD (2015) for AUD medication development: abstinence, i.e. no periods of any drinking, and no heavy drinking, i.e. no periods of heavy drinking. The following outcomes were classified as abstinence: return to any drinking and percent days abstinent. The following outcomes were classified as no heavy drinking: return to heavy drinking, percent heavy drinking days, drinks per day and drinks per drinking day. As the effect sizes for abstinence and no heavy drinking were in opposite directions, the effect sizes for abstinence were reverse-coded. This transformation allowed for the interpretation of a negative effect size to indicate that the pharmacotherapy treatment group had a lower group mean than the control group (see Ray *et al*. (2021) for details).

Two variables were selected as potential predictors of trial outcome: (a) required pre-trial abstinence, as indicated by requiring a duration of abstinence prior to study randomization for at least 1 week, based on common pre-trial abstinence duration requirements (reviewed in (Rösner *et al*., 2010a, 2010b)) and (b) required pre-trial AUD diagnosis, as indicated by a requirement of meeting an alcohol dependence diagnosis on the DSM-IV-Tr as assessed by the Structured Clinical Interview for the DSM-IV (American Psychiatric Association, 1980) or by the Mini International Neuropsychiatric Interview (Sheehan *et al*., 1998).

Data analysis

For each study, Cohen's d was calculated as the target effect size. Cohen's d is an unbiased measure of the standardized group mean difference. Cohen's d was defined as the mean from the treatment group (active medication) minus the mean from the control group (placebo) divided by a pooled standard deviation and corrected by multiplying a correction factor, $d = \left(1 - \frac{3}{4\left(n_1+n_2\right)-9}\right) \frac{\overline{y_t}-\overline{y_c}}{\sqrt{\frac{\left(n_t-1\right)s_t^2+\left(n_c-1\right)s_c^2}{n_t+n_c-2}}}$ where n_t and n_c are the sample sizes of the treatment and control groups, $\overline{y_t}$ and $\overline{y_c}$ are the sample means of the treatment and control groups and s_t^2 and s_c^2 are the sample variances of the treatment and control groups (Hedges, 1981).

Next, we conducted meta-regression, also known as mixed-effect model (Hedges and Vevea, 1998), analyses. In the meta-regression models, pre-trial abstinence and pre-trial AUD diagnosis were standardized to allow for more meaningful intercepts. To do so, Z scores for continuous predictor X were calculated as follows: (X-mean(X))/SD(X). The meta-regression analyses allowed the estimation of the population effect size when the covariates are 0 (i.e. the covariates are at their average levels) and to test the effects of pre-trial abstinence, pre-trial AUD diagnosis and their interaction on effect

sizes within the two outcomes using the *metafor* R package (Viechtbauer, 2010). We corrected for publication bias using the Vevea and Hedge's weight-function model (Vevea and Hedges, 1995), obtained the corrected estimated overall effect sizes and conducted regression analysis with the corrected estimates. Publication bias correction was conducted using the *weightr*R package (Coburn *et al*., 2019). Based on the simulation study of Du *et al.* (2017), Vevea and Hedge's weight-function model provides accurate estimates and inferences with the number of studies in the current meta-regression. To correct for multiple comparisons, the alpha level was set at 0.025, reflecting the two meta-regression analyses.

As the studies included in this meta-regression included FDA-approved medications (naltrexone and acamprosate), which have shown clinical efficacy to treat AUD, and non–FDA-approved medications, which have not definitely shown clinical efficacy to treat AUD, we conducted a sub-analysis (i.e. sensitivity analysis) of studies that tested FDA-approved medications (k = 72 studies). These analyses used identical methods to those described above.

RESULTS

Study characteristics

The 118 studies included in this study were published from 1990 to 2016. Nineteen medications were tested as follows: acamprosate (28 studies), aripiprazole (1 study), baclofen (6 studies), carbamazepine (1 study), gabapentin (5 studies), levetiracetam (3 studies), memantine (1 study), nalmefene (7 studies), naltrexone (44 studies), olanzapine (2 studies), ondansetron (1 study), quetiapine (5 studies), rimonabant (1 study), ritanserin (1 study), sertraline (1 study), topiramate (10 studies), valproate (3 studies), varenicline (4 studies) and zonisamide (2 studies). Of note, this includes studies that tested multiple medications in the same study ($n = 8$). A total of 21,032 treated participants were included in this study. The average sample size for the RCTs was 172.39 ± 186.93 (sample mean ± standard deviation; range 10–1383). The majority of the studies required an AUD diagnosis ($n = 110$; 93.2%). The majority of studies did not require abstinence prior to randomization ($n = 71$; 60.2%); a small minority of studies did not provide information regarding the requirement of abstinence prior to randomization ($n = 5$; 4.24%). The average number of drinks per month of study participants at baseline was 261.68 ± 129.25 (sample mean ± standard deviation; range 68.6–771.4).

Abstinence outcome

The estimated population effect size for the abstinence outcome was 0.17 ($P = 0.57$) when required pre-trial abstinence and required AUD diagnosis (alcohol dependence) were 0 (i.e. the average level). In other words, when the predictors were at average level, there was no significant benefit of medication over placebo on the abstinence outcome. The influence of requiring pre-trial abstinence on the abstinence outcome was non-significant ($\beta = -0.18$, $P = 0.78$). Similarly, the effect of requiring AUD to enter the study on the abstinence outcome was non-significant ($\beta = -0.05$, $P = 0.88$). The interaction between requiring pre-trial abstinence and requiring AUD diagnosis was also non-significant ($\beta = 0.12$, $P = 0.86$; see Table 1). Correcting for publication bias produced similar, non-significant results (pre-trial abstinence: $\beta = -0.33$, $P = 0.79$; pre-trial AUD diagnosis: $\beta = -0.09$, $P = 0.88$; interaction: $\beta = 0.22$, $P = 0.86$). Together, these non-significant results suggest that requiring pre-trial abstinence and AUD diagnosis did not influence the likelihood of a significant medication effect on the abstinence outcome.

Table 1. Effect of predictors on abstinence and heavy drinking outcomes

	β-Estimate	SE	*P*-value
Abstinence outcome			
Average effect (intercept)	0.17	0.30	0.57
Pre-trial abstinence required	−0.18	0.63	0.78
AUD diagnosis required	−0.05	0.31	0.88
Abstinence X AUD interaction	0.12	0.65	0.86
No heavy drinking outcome			
Average effect (intercept)	−0.20	0.12	0.10
Pre-trial abstinence required	0.19	0.30	0.53
AUD diagnosis required	−0.05	0.13	0.67
Abstinence X AUD interaction	−0.19	0.31	0.55

No heavy drinking outcome

The estimated population effect size for the no heavy drinking outcome was −0.20 ($P = 0.10$) when required pre-trial abstinence and required AUD diagnosis were 0 (i.e. the average level). In other words, when the predictors were at average level, there was no significant benefit of medication over placebo on the no heavy drinking outcome. Requiring pre-trial abstinence did not significantly alter the no heavy drinking outcome ($\beta = 0.19$, $P = 0.53$). Similarly, the effect of requiring AUD diagnosis to enter the study on the no heavy drinking outcome was non-significant ($\beta = -0.05$, $P = 0.67$). The interaction between requiring pre-trial abstinence and requiring AUD diagnosis on the no heavy drinking outcome was also non-significant ($\beta = -0.19$, $P = 0.55$; see Table 1). Correcting for publication bias produced similar, non-significant results (pre-trial abstinence: $\beta = 0.28$, $P = 0.54$; pre-trial AUD diagnosis: $\beta = -0.08$, $P = 0.66$; interaction: $\beta = 0.29$, $P = 0.55$). Together, these non-significant results suggest that requiring pre-trial abstinence and requiring AUD diagnosis also did not influence the likelihood of a significant medication effect on the no heavy drinking outcome.

FDA-approved medications only

The sub-analysis included 72 studies that investigated naltrexone and acamprosate, FDA-approved medications for AUD. Similar to what was found for the whole dataset (approved and non-approved medications), non-significant results were found for both drinking outcomes (see Table 2).

For the abstinence outcome, the estimated population effect size when required pre-trial abstinence and required pre-trial AUD diagnosis were 0 was 0.21, $P = 0.64$. The effect of requiring pre-trial abstinence on the abstinence outcome was non-significant ($\beta = -0.22$, $P = 0.78$). Similarly, the effect of requiring AUD diagnosis to enter the study on the abstinence outcome was non-significant ($\beta = 0.01$, $P = 0.99$). The interaction between requiring pre-trial abstinence and requiring AUD diagnosis on the abstinence outcome was also non-significant ($\beta = 0.09$, $P = 0.92$; see Table 2). Correcting for publication bias produced similar, non-significant results (pre-trial abstinence: $\beta = -0.44$, $P = 0.77$; pre-trial AUD diagnosis: $\beta = 0.01$, $P = 0.99$; interaction: $\beta = 0.17$, $P = 0.91$).

Table 2. Effect of predictors on abstinence and heavy drinking outcomes in FDA-approved medications only

	β-Estimate	SE	*P*-value
Abstinence outcome			
Average effect (intercept)	0.21	0.46	0.64
Pre-trial abstinence required	−0.22	0.79	0.77
AUD diagnosis required	0.009	0.48	0.99
Abstinence X AUD interaction	0.09	0.81	0.92
No heavy drinking outcome			
Average effect (intercept)	−0.02	0.16	0.92
Pre-trial abstinence required	0.007	0.26	0.98
AUD diagnosis required	−0.20	0.17	0.25
Abstinence X AUD interaction	−0.06	0.27	0.83

For the no heavy drinking outcome, the estimated population effect size when required pre-trial abstinence and required pre-trial AUD diagnosis were at average levels was −0.02, $P = 0.92$. The effect of requiring pre-trial abstinence on the no heavy drinking outcome was non-significant ($\beta = 0.01$, $P = 0.8$). Similarly, the effect of requiring AUD diagnosis to enter the study on the no heavy drinking outcome was non-significant ($\beta = -0.20$, $P = 0.25$). The interaction between required pre-trial abstinence and required AUD diagnosis on the no heavy drinking outcome was also non-significant ($\beta = -0.06$, $P = 0.83$; see Table 2). Correcting for publication bias produced similar, non-significant results (pre-trial abstinence: $\beta = 0.12$, $P = 0.83$; pre-trial AUD diagnosis: $\beta = -0.37$, $P = 0.22$; interaction: $\beta = -0.19$, $P = 0.74$).

DISCUSSION

Design features for AUD clinical trials have been subjected to scientific scrutiny as enhanced methodology is associated with greater likelihood of a significant medication effect (Miller and Wilbourne, 2002). Recent qualitative reviews have put forth recommendations for best practices in the design and execution of AUD clinical trials (Witkiewitz *et al.*, 2015a). The present study examined two variables representing design decisions in AUD trials, namely requiring pre-trial abstinence and pre-trial AUD diagnosis. Results of this meta-regression found that neither variable predicted the likelihood of obtaining a significant medication effect in the trial. This is highly relevant as these design features may have a large impact on the implementation of the trial as well as the generalizability of the results.

With regard to the requirement for AUD diagnosis, it may be that since the majority of studies required the diagnosis ($n = 110$; 93.2%), the difference was not detected due to an imbalance between trials requiring and not requiring pre-trial abstinence. This requirement remains important and it may be that by virtue of seeking treatment, individuals are much more likely to report an AUD (Venegas *et al.*, 2021). It may also be that for the purpose of FDA approval of a compound, an AUD diagnosis enhances the case for the AUD indication. Nevertheless, medication trials that do not require an AUD diagnosis may also be helpful in expanding the utility of pharmacotherapies for heavy drinkers without AUD. Notably, only 1.6% of adults with a past-year AUD received an FDA-approved medication to treat their AUD (Han *et al.*, 2021).

With regard to requiring pre-trial abstinence, the majority of studies did not require a pre-trial abstinence duration of at least one week ($n = 71$; 60.2%). Nevertheless, studies have shown that participants reduce their drinking in anticipation of research studies involving alcohol, including both treatment (Stasiewicz *et al.*, 2019) and non-treatment studies (Baskerville *et al.*, 2021). Importantly, the mechanism of action of specific pharmacotherapies may influence the requirement of pre-trial abstinence. For example, injectable extended-release naltrexone has been found to be more effective for patients who were abstinent prior to treatment initiation (O'Malley *et al.*, 2007); therefore, medications with similar mechanisms of action may include a required pre-trial abstinence criterion as a design feature in order to improve the likelihood of identifying a treatment effect. A related concern has to do with pharmacotherapy studies excluding individuals who have made pre-trial changes in drinking and have been abstinent for too long. Many studies will have a window of abstinence requirement with a larger-than-allowed abstinence period leading to the exclusion of a research participant. While the present study is not able to examine a more nuanced 'and U-shaped' effect of abstinence requirement, the underlying dimensionality of the pre-trial abstinence requirement period should be considered.

In terms of trial endpoints, this study utilized the FDA-recommended outcomes of abstinence and no heavy drinking. Critically, a recent review of ongoing AUD clinical pharmacotherapy trials reported that only 8% of trials (4/50) had an FDA-recommended primary outcome (i.e. abstinence or no heavy drinking), while only 12% of trials (6/50) had an FDA-recommended secondary outcome (i.e. percentage of heavy drinking days) (Wallach *et al.*, 2020). Given this low usage, it is possible that we did not detect significant effects of these design features due to our selection of endpoints, which reflects the status of the literature and the outcomes reported/available for analysis. Nevertheless, the registered outcomes in ongoing clinical trials for AUD may reflect a growing interest in the field for non-abstinence outcomes, including the push toward using reductions in drinking risk levels as endpoints in alcohol pharmacotherapy trials (Falk *et al.*, 2019).

This study has a several limitations that should be applied to the interpretation of the results. First, the coding for this meta-regression defined the requirement of pre-trial abstinence as studies with an inclusion criterion of an abstinence period of at least one week prior to randomization. As a result of this coding definition, some studies that required a shorter period of abstinence, e.g. less than one week, would have been coded as not requiring pre-trial abstinence. Future studies should examine the abstinence window with a non-binary yes/no lens to determine the impact of length of pre-trial abstinence on treatment outcomes. Relatedly, coding for this meta-regression considered drinks per day and drinks per drinking day as heavy drinking outcomes. We chose to include these consumption outcomes in addition to return to heavy drinking and percent heavy drinking days as frequency and quantity of drinking are often reported in clinical trials. Therefore, the inclusion of consumption outcomes increased the amount of data available for this meta-regression. However, the inclusion of these outcomes may have resulted in overlap between the abstinence and no heavy drinking outcomes. Future studies should separate the consumption outcomes to test this effect directly. Additionally, while this study examined the effect of two critical design features in AUD clinical trials, it could not test a wider set of critical design features such as baseline

drinking levels, severity of AUD and presence of comorbid psychiatric or substance use disorders. These variables were captured in our coding system, yet due to low levels of reporting, the final dataset did not provide the representative sample that is required for the proposed analysis. These predictors may impact the efficacy of AUD clinical trials or may interact with pre-trial abstinence or AUD diagnosis requirements. Of particular note, a recent meta-regression of 19 RCTs found that baseline severity of AUD influenced the placebo response, such that mild-severity studies had a higher placebo-response than high severity studies (Scherrer *et al.*, 2021). We were unable to capture measures of severity, including number of diagnoses, amount of alcohol consumed and questionnaires assessing severity in the present meta-regression. The variability in reporting of AUD clinical trial features, which we encountered in this meta-analysis, is underscored in the recent review of ongoing clinical trials (Wallach *et al.*, 2020) and in a manuscript on guidelines for clinical trials reporting (Witkiewitz *et al.*, 2015b). Therefore, our study provides yet another example of the need for standardized reporting and we echo the recommendations provided by (Witkiewitz *et al.*, 2015a) as a solution to the incomplete reporting practices that limit data integrative methods such as meta-analysis and meta-regression. Relatedly, this study did not test the effect of design features on harm reduction endpoints, as they are not currently approved as primary efficacy endpoints by the FDA. However, there is substantial interest in the field in these endpoints and future studies should examine the effect of design features on harm reduction outcomes. Additionally, as this study was a secondary data analysis, only medications that were tested in behavioral pharmacology and randomized controlled trials were included in the literature search. Some medications, including disulfiram, were not tested in behavioral pharmacology studies and therefore were excluded from this study. Future analyses of RCT data should include all medications tested in the RCT study format.

In conclusion, by examining two AUD clinical trial design features (i.e. pre-trial abstinence requirement and AUD diagnosis requirement) in a quantitative, rather than qualitative, fashion, the present study advances the literature and shows that requiring AUD diagnosis or pre-trial abstinence does not impact the likelihood of a significant medication effect in the trial. Clearly, these design features operate in conjunction with other best practices (Witkiewitz *et al.*, 2015a) and while interactive effects were not found, it may be that an overall trial quality index is the key determinant of reliable results (Miller and Wilbourne, 2002), as opposed to any one design feature alone, which may not have a large enough effect on the likelihood of detecting a medication effect. Lastly, more comprehensive analysis of clinical trial characteristics and their impact on outcomes would be greatly aided by consisted reporting practices in our field.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

FUNDING

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (K24AA025704 to L.A.R.). S.D. was supported by a training grant from the National Institute on Drug Abuse (T32DA024635). The funders had no role in the design, analysis, interpretation or writing of the report. None of the authors have any competing financial interest in relation to this work. None of the authors have any conflict of interests.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interests.

References

Administration FaD. (2015) *Alcoholism: Developing Drugs for Treatment*. Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852: Center for Drug Evaluation and Research (CDER).

American Psychiatric Association A. (1980) *Diagnostic and Statistical Manual of Mental Disorders*, Vol. **3**. Washington, DC: American Psychiatric Association.

Anton RF, Litten RZ, Falk DE, *et al.* (2012) The alcohol clinical trials initiative (ACTIVE): purpose and goals for assessing important and salient issues for medications development in alcohol use disorders. *Neuropsychopharmacology* **37**:402–11.

Baskerville WA, Nieto SJ, Ho D, *et al.* (2021) Baseline drinking patterns in non-treatment seeking problem drinkers. *Alcohol Alcohol (Oxford, Oxfordshire)* **56**:57–63.

Begg C, Cho M, Eastwood S, *et al.* (1996) Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* **276**:637–9.

Coburn KM, Vevea JL, Coburn MKM. (2019) Package 'weightr'. In *Estimating Weight-Function Models for Publication Bias*.

Du H, Liu F, Wang L. (2017) A Bayesian "fill-in" method for correcting for publication bias in meta-analysis. *Psychol Methods* **22**:799–817.

Falk D, Wang XQ, Liu L, *et al.* (2010) Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. *Alcohol Clin Exp Res* **34**:2022–34.

Falk DE, Litten RZ, Anton RF, *et al.* (2014) Cumulative proportion of responders analysis (CPRA) as a tool to assess treatment outcome in alcohol clinical trials. *J Stud Alcohol Drugs* **75**:335–46.

Falk DE, O'Malley SS, Witkiewitz K, *et al.* (2019) Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. *JAMA Psychiat* **76**:374–81.

Feinn R, Kranzler HR. (2005) Does effect size in naltrexone trials for alcohol dependence differ for single-site vs. multi-center studies? *Alcohol Clin Exp Res* **29**:983–8.

Hallgren KA, Witkiewitz K, Kranzler HR, *et al.* (2016) Missing data in alcohol clinical trials with binary outcomes. *Alcohol Clin Exp Res* **40**:1548–57.

Han B, Jones CM, Einstein EB, *et al.* (2021) Use of medications for alcohol use disorder in the US: results from the 2019 National Survey on drug use and health. *JAMA Psychiat* **78**:922–4.

Hedges LV. (1981) Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Stat* **6**:107–28.

Hedges LV, Vevea JL. (1998) Fixed-and random-effects models in meta-analysis. *Psychol Methods* **3**:486–504.

Humphreys K, Weisner C. (2000) Use of exclusion criteria in selecting research subjects and its effect on the generalizability of alcohol treatment outcome studies. *Am J Psychiatry* **157**:588–94.

Humphreys K, Harris AH, Weingardt KR. (2008) Subject eligibility criteria can substantially influence the results of alcohol-treatment outcome research. *J Stud Alcohol Drugs* **69**:757–64.

Jonas DE, Amick HR, Feltner C, *et al.* (2014) Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* **311**:1889–900.

Kaitin KI, Milne CP. (2011) A dearth of new meds. *Sci Am* **305**:16.

Litten RZ, Egli M, Heilig M, *et al.* (2012) Medications development to treat alcohol dependence: a vision for the next decade. *Addict Biol* **17**:513–27.

Litten RZ, Falk DE, Ryan ML, *et al.* (2016) Discovery, development, and adoption of medications to treat alcohol use disorder: goals for the phases of medications development. *Alcohol Clin Exp Res* **40**: 1368–79.

Miller WR, Wilbourne PL. (2002) Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* **97**:265–77.

O'Malley SS, Garbutt JC, Gastfriend DR, *et al.* (2007) Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *J Clin Psychopharmacol* **27**:507–12.

Ray LA, Bujarski S, Yardley MM, *et al.* (2017) Differences between treatment-seeking and non-treatment-seeking participants in medication studies for alcoholism: do they matter? *Am J Drug Alcohol Abuse* **43**:703–10.

Ray LA, Bujarski S, Roche DJO, *et al.* (2018) Overcoming the "valley of death" in medications development for alcohol use disorder. *Alcohol Clin Exp Res* **42**:1612–22.

Ray LA, Du H, Green R, *et al.* (2021) Do behavioral pharmacology findings predict clinical trial outcomes? A proof-of-concept in medication development for alcohol use disorder. *Neuropsychopharmacology* **46**:519–27.

Rohn MC, Lee MR, Kleuter SB, *et al.* (2017) Differences between treatment-seeking and nontreatment-seeking alcohol-dependent research participants: an exploratory analysis. *Alcohol Clin Exp Res* **41**:414–20.

Rösner S, Hackl-Herrwerth A, Leucht S, *et al.* (2010a) Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* Cd004332. https://doi.org/10.1002/14651858.CD004332.pub2.

Rösner S, Hackl-Herrwerth A, Leucht S, *et al.* (2010) Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* (12):Cd001867. https://doi.org/10.1002/14651858.CD001867.pub3.

Scherrer B, Guiraud J, Addolorato G, *et al.* (2021) Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: a meta-regression analysis to develop an enrichment strategy. *Alcohol Clin Exp Res* **45**:1722–34.

Schulz KF, Chalmers I, Hayes RJ, *et al.* (1995) Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* **273**: 408–12.

Sheehan DV, Lecrubier Y, Sheehan KH, *et al.* (1998) The MINI-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* **59**:22–33.

Stasiewicz PR, Bradizza CM, Ruszczyk MU, *et al.* (2019) The identification of Pretreatment trajectories of alcohol use and their relationship to treatment outcome in men and women with alcohol use disorder. *Alcohol Clin Exp Res* **43**:2637–48.

Venegas A, Donato S, Meredith LR, *et al.* (2021) Understanding low treatment seeking rates for alcohol use disorder: a narrative review of the literature and opportunities for improvement. *Am J Drug Alcohol Abuse* **47**:664–79.

Vevea JL, Hedges LV. (1995) A general linear model for estimating effect size in the presence of publication bias. *Psychometrika* **60**: 419–35.

Viechtbauer W. (2010) Conducting meta-analyses in R with the metafor package. *J Stat Softw* **36**:1–48.

Wallach JD, Krystal JH, Ross JS, *et al.* (2020) Characteristics of ongoing clinical trials for alcohol use disorder registered on ClinicalTrials.Gov. *JAMA Psychiat* **77**:1081–4.

Witkiewitz K, Falk DE, Kranzler HR, *et al.* (2014) Methods to analyze treatment effects in the presence of missing data for a continuous heavy drinking outcome measure when participants drop out from treatment in alcohol clinical trials. *Alcohol Clin Exp Res* **38**: 2826–34.

Witkiewitz K, Finney JW, Harris AH, *et al.* (2015a) Recommendations for the design and analysis of treatment trials for alcohol use disorders. *Alcohol Clin Exp Res* **39**:1557–70.

Witkiewitz K, Finney JW, Harris AHS, *et al.* (2015b) Guidelines for the reporting of treatment trials for alcohol use disorders. *Alcohol Clin Exp Res* **39**:1571–81.