See commentary by Shale and Atherton

Generalizability of Pharmacologic and Psychotherapy Clinical Trial Results for Posttraumatic Stress Disorder to Community Samples

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ABSTRACT

Objective: The present study sought to quantify the generalizability of pharmacologic and psychotherapy clinical trial results in individuals with a *DSM-IV* diagnosis of posttraumatic stress disorder (PTSD) to a large representative community sample.

Methods: Data were derived from the 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large nationally representative sample of the adult US population. We applied a standard set of exclusion criteria representative of pharmacologic and psychotherapy clinical trials to all adults with a *DSM-IV* diagnosis of PTSD in the previous 12 months (n = 1,715) and then to a subsample of participants seeking treatment (n = 366). Our aim was to assess how many participants with PTSD would fulfill typical eligibility criteria.

Results: We found that more than 6 of 10 respondents from the overall PTSD sample and more than 7 of 10 respondents seeking treatment for PTSD would have been excluded by 1 exclusion criterion or more in a typical pharmacologic trial. In contrast, about 2 of 10 participants in the full sample and about 3 of 10 participants seeking treatment for PTSD would have been excluded in a typical psychotherapy efficacy trial.

Conclusions: We found that psychotherapy trial results may be applied to most patients with PTSD in routine clinical practice. The designers of pharmacologic clinical trials should carefully consider the trade-offs between the application of each exclusion criterion and its impact on representativeness. Specification a priori of the goals of the study, better justification for each exclusion criterion, and estimation of the proportion of individuals ineligible for the trial would assist study design. Developing integrated forms of pharmacotherapy and psychotherapy that simultaneously target commonly overlapping psychiatric disorders may yield more informative results for mental health care providers and research funding agencies.

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Randomized controlled clinical trials (RCTs) are often considered the "gold standard" for assessing the efficacy of pharmacologic and psychotherapeutic interventions in clinical research.[1] RCTs apply restrictive eligibility criteria in hope of decreasing heterogeneity in response to treatment (and thereby increasing statistical power), reducing study costs (eg, by excluding participants who are likely to drop out prematurely), ensuring safety of participants (eg, excluding those who could be harmed in the study), and complying with guidelines by regulatory agencies.[2] However, the high internal validity of clinical trials may be achieved at the cost of diminished external validity (ie, applicability of clinical trial results to routine clinical care) because a substantial proportion of treatment-seeking individuals who are excluded from trials may respond differently to the studied intervention.[3] Therefore, there have been calls[3–5] to quantify the generalizability of clinical trials to the broader target population to help frontline practitioners determine the relevance of these studies for their patients and to assist research funding agencies identify gaps in knowledge.

Previous studies have estimated the impact of exclusion criteria on the generalizability of clinical trials for several psychiatric disorders, including bipolar disorder,[6] panic disorder,[7] major depressive disorder (MDD),[8–12] generalized anxiety disorder,[13] schizophrenia,[14–17] borderline personality disorder,[1] social anxiety disorder,[18] alcohol dependence,[19,20] nicotine dependence,[21] and cannabis dependence.[22] These studies concluded that the rate of exclusion would range from 50.5% to 87.8%, suggesting limited applicability of clinical trial results to patients seen in routine clinical settings.

Despite the important personal suffering and societal burden associated with posttraumatic stress disorder (PTSD) and the need for more effective treatments,[23–26] no study to our knowledge has examined the representativeness of pharmacologic clinical trials for PTSD, and only one[27] has focused on the generalizability of psychotherapy clinical trials. Given the high prevalence of psychiatric and medical comorbidities associated with PTSD,[28–34] it is important to examine the generalizability of pharmacologic and psychotherapy trials for PTSD to evaluate the relevance of applying their results to patients in day-to-day clinical practice and guide eligibility criteria selection of future clinical trials.

In the present report, we use the population generalizability estimator method,[10,20] which applies exclusion criteria commonly used in pharmacologic and psychotherapy clinical

Clinical Points

- Exclusion criteria applied in pharmacologic clinical trials for PTSD exclude a majority of participants, particularly those seeking treatment, limiting the generalizability of the trial results.
- Psychotherapy trial results may be applied to most patients with PTSD in routine clinical practice.
- Clinicians and researchers should carefully consider eligibility criteria and their impact on the representativeness of clinical trials for PTSD.

trials for PTSD to a nationally representative sample to assess the generalizability of the criteria to community adults with PTSD.

METHODS

Sample

Data were drawn from the 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the second wave that follows upon the Wave 1 NESARC, which was conducted in 2001–2002 and described in detail elsewhere.[35,36] The Wave 1 NESARC is a nationally representative face-to-face survey of 43,093 civilian noninstitutionalized US residents aged 18 years and older conducted by the US Census Bureau under the direction of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The cumulative response rate at Wave 2 was 70.2%, reflecting 34,653 who completed interviews in both Waves. The Wave 2 NESARC data were weighted to reflect design characteristics of the NESARC survey, to adjust for Wave 2 nonresponse, to account for oversampling, and to be representative of the US population.[37] The research protocol, including informed consent procedures, received full human subjects review and approval from the US Census Bureau and US Office of Management and Budget.

Assessment of PTSD

Diagnoses were made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV), a computerized, fully structured instrument designed for experienced nonclinician interviewers.[36]

PTSD was diagnosed when respondents endorsed at least 1 symptom within Criterion B, at least 3 within Criterion C, and at least 2 within Criterion D, lasting at least 1 month (Criterion E), *subsequent to* the worst event they experienced that involved intense fear, helplessness, or horror, and the belief that they or someone close to them might die or be seriously injured or permanently disabled. Diagnoses of PTSD also required that the *DSM-IV* clinical significance criterion of impairment or distress (Criterion F) be met. Respondents with PTSD occurring the year preceding the Wave 2 interview were considered as having a current PTSD, the time frame used by the AUDADIS-IV when assessing the presence of "current" symptoms. A participant with a 12-month *DSM-IV* diagnosis of PTSD was defined as seeking treatment if she/he "went anywhere/had seen anyone to get help with reactions to stressful events" in the previous 12 months. Test-retest reliability of PTSD diagnoses was good ($\kappa = 0.64$).[38] Reliability ($\kappa > 0.74$) was good to excellent for substance use disorders and fair to good for mood and other anxiety disorders ($\kappa = 0.40–0.64$).

Measures

Exclusion criteria commonly used in pharmacologic and psychotherapy clinical trials for PTSD were applied to a sample representative of the general US population to evaluate the proportion of participants with a *DSM-IV* diagnosis of PTSD that would be eligible for a typical pharmacologic and psychotherapy clinical trial. The same criteria were applied to a subsample of participants seeking treatment for PTSD to investigate potential differences in eligibility between treatment-seeking and non-treatment–seeking individuals.

We collected the exclusion criteria from clinical trials for PTSD included in a recent meta-analysis[39] examining the effects of pharmacologic treatments on PTSD and extracted the psychotherapy clinical trials from a recent meta-analysis[40] of the efficacy of treatments for PTSD. All the 37 trials used in the pharmacologic meta-analysis and the 56 trials used in the psychotherapy meta-analysis were included in the present study. Two coders (S.F. and N.H.) independently collected all exclusion criteria from the 37 pharmacologic trials and the 56 psychotherapy trials (Table 1). Interrater reliability was adequate (intraclass correlation coefficient = 0.87) and disagreement was resolved by consensus. The median number of exclusion criteria was 10 in the pharmacologic trials (of which 8 could be operationalized) and 4 in the psychotherapy trials (of which all could be operationalized). To estimate the representativeness of typical pharmacologic and psychotherapy clinical trials with traditional exclusion criteria, we applied respectively the 10 and the 4 most commonly used criteria to all individuals with a *DSM-IV* diagnosis of PTSD within the previous 12 months to the NESARC sample (Tables 2 and 3).

We operationalized exclusion criteria to be consistent with prior work.[10,20] The criteria "current major depressive episode," "lifetime bipolar disorder," "current drug abuse or dependence," and "current alcohol abuse or dependence" were diagnosed following *DSM-IV* criteria. The criterion "significant risk of suicide" was considered met if the person reported a suicide attempt during the previous year. The criterion "current psychotic features" was assessed by a single question: "Did a doctor or other health professional ever diagnose you with schizophrenia or psychotic illness or episode during the last year?" The criterion "pregnancy or lactating" was assessed by the following question: "Were you pregnant during the past year?" The criterion "significant medical condition" was approximated using several questions on 12-month angina pectoris, myocardial infarction, or any other form of heart disease, diabetes mellitus, stroke, or cirrhosis or hepatic disease and was considered met if the

Table 1. Exclusion Criteria in 37 Pharmacologic and 56 Psychotherapy Clinical Trials Examining the Respective Effects of Treatments on Posttraumatic Stress Disorder (PTSD)[a]

Exclusion Criteria Present in More Than 10% of Pharmacologic Trials or Psychotherapy Trials or Both	Percentage and Number of Studies Using the Exclusion Criteria		Comparing the Frequency of the Use of Each Criterion, χ^2 (*P* Value)
	Pharmacologic Trials (no. = 37), % (no.)	Psychotherapy Trials (no. = 56), % (no.)	
Current drug abuse or dependence	81.1% (30)	64.3% (36)	2.3 (.13)
Current alcohol abuse or dependence	81.1% (30)	64.3% (36)	2.3 (.13)
Current psychotic features	70.3% (26)	84.0% (47)	1.7 (.19)
Lifetime bipolar disorder	67.6% (25)	25.0% (14)	**14.9 (<.01)**
Significant medical conditions	62.2% (23)	10.7% (6)	**25.1 (<.01)**
Currently taking psychotropic medication	51.4% (19)	21.4% (12)	**7.7 (<.01)**
Current major depressive episode	40.5% (15)	5.4% (3)	**15.5 (<.01)**
Significant risk of suicide	40.5% (15)	55.4% (31)	1.41 (.24)
Currently receiving psychotherapy	40.5% (15)	14.3% (8)	**6.9 (<.01)**
Neurologic diseases	32.4% (12)	30.4% (17)	0.05 (.83)
Pregnancy or lactating	43.2% (16)	…	na
Current panic disorder	35.1% (13)	…	na
Current generalized anxiety disorder	29.7% (11)	…	na
Current specific phobia	29.7% (11)	…	na
Current social anxiety disorder	27.0% (10)	…	na
Current dysthymia	21.6% (8)	…	na
Current obsessive-compulsive disorder	21.6% (8)	…	na
Mental retardation	…	16.1% (9)	na
Ongoing domestic violence	…	14.3% (8)	na
History of any dissociative disorder	…	12.5% (7)	na
Any personality disorder	…	10.7% (6)	na

[a]Boldface type indicates statistical significance.
Abbreviation: na = not applicable. Symbol: … = criteria not used or used in less than 10% of trials.

diagnosis was confirmed by a physician. Information to approximate the criteria "currently taking any psychotropic medication," "currently receiving psychotherapy," and "neurological disease" was not available in NESARC.

Analysis Methods

We first determined the percentages (and their 95% confidence intervals [CI]) of survey participants with a current *DSM-IV* diagnosis of PTSD who would have been excluded by individually applying each exclusion criterion in pharmacologic and psychotherapy clinical trials for PTSD. 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. We conducted these analyses for all participants with a 12-month *DSM-IV* diagnosis of PTSD (n = 1,715), and for the subsample of individuals who sought treatment (n = 366), in trials examining the effects of pharmacologic and psychological treatments on PTSD separately. Weighted prevalence estimates and their 95% CIs were computed using SUDAAN 10 (RTI International, Research Triangle Park, North Carolina) to account for the complex sampling design of the NESARC.

RESULTS

Exclusion Criteria

Several exclusion criteria were applied in pharmacologic and psychotherapy clinical trials, ie, current drug abuse or dependence, current alcohol abuse or dependence, current psychotic features, lifetime bipolar disorder, significant medical conditions, currently taking psychotropic medication, current major depressive episode, significant risk of suicide, currently receiving psychotherapy, and neurologic disease (Table 1). Among these criteria, 5 were significantly more commonly used in pharmacologic trials than in psychotherapy clinical trials, ie, lifetime bipolar disorder, significant medical conditions, currently taking psychotropic medications, current major depressive episode, and currently receiving psychotherapy. Frequency of use of other criteria did not differ statistically between pharmacologic and psychotherapy trials. In addition, several criteria were typically applied only in pharmacologic trials (ie, current panic disorder, current generalized anxiety disorder, current specific phobia, current social anxiety disorder, current dysthymia, current obsessive-compulsive disorder, and pregnancy or lactating) or only in psychotherapy trials (ie, history of any dissociative disorder, any personality disorder, mental retardation, and ongoing domestic violence). The median number of exclusion criteria used in pharmacologic trials was higher than in psychotherapy trials for PTSD (10 vs 4).

Participants With 12-Month PTSD

Of the 1,715 participants who met *DSM-IV* criteria for PTSD during the previous year, 63.8% (95% CI, 60.8%–66.6%) would have been excluded by at least 1 of the 8 most common and operationalizable criteria in pharmacologic efficacy trials (Table 2). By contrast, the percentage of exclusion by at least 1 of the 4 most common and operationalized criteria in psychotherapy efficacy trials was 19.1% (95% CI, 16.8%–21.7%) (Table 3).

Table 2. Pharmacologic Treatments for PTSD: Estimated Percentage of Adults With Posttraumatic Stress Disorder (PTSD) in Wave 2 NESARC Excluded From Typical Clinical Trials by Traditional Exclusion Criteria

	12-Month PTSD (n = 1,715)		Treatment-Seeking Subsample (n = 366)	
Exclusion Criteria[a]	%[b]	95% CI	%[b]	95% CI
Current drug abuse or dependence	6.89	5.41–8.73	7.98	5.24–11.95
Current alcohol abuse or dependence	13.23	11.36–15.35	16.02	12.00–21.05
Current psychotic features	3.50	2.51–4.87	8.48	5.65–12.56
Lifetime bipolar disorder	25.68	23.05–28.50	33.41	27.67–39.68
Significant medical conditions	22.37	20.06–24.86	25.60	20.54–31.41
Currently taking psychotropic medication		NA		NA
Pregnancy or lactating	3.95	2.96–5.27	2.14	0.98–4.60
Current major depressive episode	18.94	16.82–21.26	26.11	21.21–31.68
Significant risk of suicide	0.88	0.41–1.87	1.58	0.57–4.29
Currently receiving psychotherapy		NA		NA
Exclusion by at least 1 criterion	63.75	60.84–66.57	75.10	69.50–79.97

[a]Derived from the review of 37 clinical trials.
[b]Percentages are weighted values. Criteria are ranked by their frequency in typical clinical trials of pharmacologic treatments for PTSD.
Abbreviations: NA = not available in NESARC, NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

Table 3. Psychotherapy Treatments for PTSD: Estimated Percentage of Adults With Posttraumatic Stress Disorder (PTSD) in Wave 2 NESARC Excluded From Typical Clinical Trials by Traditional Exclusion Criteria

	12-Month PTSD (n = 1,715)		Treatment-Seeking Subsample (n = 366)	
Exclusion Criteria[a]	%[b]	95% CI	%[b]	95% CI
Current psychotic features	3.50	2.51–4.87	8.48	5.65–12.56
Current drug abuse or dependence	6.89	5.41–8.73	7.98	5.24–11.95
Current alcohol abuse or dependence	13.23	11.36–15.35	16.02	12.00–21.05
Significant risk of suicide	0.88	0.41–1.87	1.58	0.57–4.29
Exclusion by at least 1 criterion	19.11	16.76–21.70	27.04	21.81–33.00

[a]Derived from the review of 56 clinical trials.
[b]Percentages are weighted values. Criteria are ranked by their frequency in typical clinical trials of psychotherapeutic treatments for PTSD.
Abbreviation: NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

In pharmacologic efficacy trials, the percentage of PTSD participants excluded by a single criterion ranged from 0.9% ("significant risk of suicide") to 25.7% ("lifetime bipolar disorder"). In psychotherapy efficacy trials, this percentage ranged from 0.9% ("significant risk of suicide") to 13.2% ("current alcohol abuse or dependence"). In pharmacologic trials, lifetime bipolar disorder, significant medical conditions, and current major depressive episode were the criteria that excluded the greatest proportion of participants with PTSD, whereas having a significant risk of suicide excluded the smallest percentage of individuals. In psychotherapy trials, having drug and alcohol abuse or dependence excluded the greatest number of individuals with PTSD, whereas the criterion "significant risk of suicide" led to the lowest exclusion rate among these participants.

Treatment-Seeking Subsample

Among the 366 participants seeking treatment, the overall exclusion rate was slightly greater, rising to 75.1% (95% CI, 69.5%–80.0%) in pharmacologic efficacy trials and 27% (95% CI, 21.8%–33.0%) in psychotherapy efficacy trials. The percentage of participants excluded by a single criterion ranged from 1.6% ("significant risk of suicide") in pharmacologic and psychotherapy trials to 33.4% ("lifetime bipolar disorder") in pharmacologic trials and 16.0% ("current alcohol abuse") in psychotherapy trials.

DISCUSSION

Our study shows that in a typical pharmacologic trial, more than 6 of 10 adults with PTSD in the full sample and more than 7 of 10 respondents in the treatment-seeking subsample would have been excluded by 1 exclusion criterion or more. In contrast, we found that approximately 2 of 10 participants in the full sample and 3 of 10 in the treatment-seeking subsample would have been excluded from participation in a typical psychotherapy trial for PTSD.

These findings indicate that traditional criteria used in pharmacologic trials for PTSD tend to exclude the majority of individuals from participation. A lifetime history of bipolar disorder, significant medical conditions, and current major depressive episode explained a large

proportion of ineligibility in pharmacologic trials for PTSD. These exclusion rates in PTSD pharmacologic trials were consistent with previous generalizability studies in adult samples examining the representativeness of clinical trials for a wide range of disorders,[1,7,10,13,22] in which 60% of the target populations was found to be ineligible. Our result suggests that pharmacologic clinical trials for PTSD may often have limited external validity since they tend to recruit samples of "pure" patients with an uncomplicated diagnosis of PTSD rather than "typical" patients who generally suffer from additional disorders. Pharmacologic clinical trial results for PTSD may thus not be readily generalizable either to community samples or to treatment-seeking populations.

By contrast, we found that psychotherapy efficacy trials for PTSD would typically include most individuals with PTSD with an exclusion rate of approximately 20% in the general population with PTSD and approximately 30% in the treatment-seeking subsample. These estimations rates are in line with those of a recent meta-analysis of psychotherapy trials for PTSD[27] that found that clinical trials included roughly 70% of patients referred for treatment and are lower than those reported in psychotherapy trials for other disorders such as generalized anxiety disorder,[13] social anxiety disorder,[18] and borderline personality disorder[1]; in those trials a majority of the target population was found to be excluded. From a public health perspective, this result suggests that efficacy observed in psychotherapy trials for PTSD may reasonably reflect the "true" effect of psychotherapy treatments for PTSD in the general population of individuals with PTSD, although further evidence may be desirable, particularly regarding individuals with comorbid PTSD and substance use disorders who typically are absent from these trials.

The higher overall exclusion rate found in pharmacologic than in psychotherapy trials may be explained by the lower number of exclusion criteria applied and the lower use of criteria excluding participants with comorbid Axis I disorder. Investigators conducting pharmacologic trials may seek to restrict their target populations to decrease potential health hazards for their patients. While some exclusion criteria are necessary in pharmacologic trials to ensure the safety of the study participants (eg, pregnancy and lactation, significant medical conditions, avoiding dangerous interactions of medications), others may be only perpetuated by convention in pharmacologic trials (eg, having a current history of major depressive episode or substance use disorders) and can dramatically narrow the population of eligible participants and thereby negatively impact on external validity. The use of narrow exclusion criteria may sometimes be viewed as a way to support the specificity of the intervention for PTSD. However, psychiatric disorders, which are highly comorbid, are increasingly conceptualized as manifestations of broad liabilities rather than discrete entities,[41–43] and several evidence-based, integrated psychotherapies have already been developed for the treatment of comorbid PTSD/MDD,[44–46] possibly explaining the global lower use of exclusion criteria in psychotherapy than in pharmacologic trials for PTSD. Integrated forms of pharmacotherapy that target commonly co-occurring disorders may hold promise for a greater number of individuals with mental disorders and may favor greater inclusive rates of patients with PTSD.[44,47]

Applying exclusion criteria to the treatment-seeking subsample excluded substantially more participants in pharmacologic and psychotherapy trials for PTSD. As previously suggested,[48] this result supports that individuals seeking treatment may present greater illness severity and more psychiatric and medical comorbidities, which may possibly lead to higher perceived need of care.[49] Paradoxically, clinical trials may tend to exclude preferentially individuals who have the greatest overall disease severity and therefore the greatest need for treatment. More inclusive eligibility criteria (particularly with the inclusion of individuals with multiple psychiatric comorbidities) would yield more informative results for mental health care providers and research funding agencies.[1,50]

This study has several limitations. First, we adopted specific conventions to apply a standard set of exclusion criteria to the NESARC sample. We considered exclusion criteria from 37 pharmacologic and 56 psychotherapy clinical trials for PTSD included in 2 recent meta-analyses.[27,39] Other conventions might have yielded different exclusion estimates. For example, the 12-month timeframe used in the AUDADIS-IV assessment of "current" symptoms could have led to an overestimation of the exclusion rates. On the other hand, 2 of the traditional exclusion criteria from pharmacologic clinical trials (ie, "currently taking any psychotropic medication" and "currently receiving psychotherapy") could not be operationalized using the NESARC and may have led to an underestimation of participants excluded from pharmacologic clinical trials. Second, participants with current PTSD who sought help for reactions to stressful events during the year preceding the interview were classified as treatment-seeking for PTSD. This definition may have included some participants seeking help for other disorders. Finally, our approach focused on the a priori eligibility of participants and was based on national epidemiologic data. It provides no information on individuals who actually enter those studies. In fact, a substantial proportion of eligible individuals may be unwilling to participate. However, the proportion of individuals that would have been eligible for psychotherapy efficacy trials for PTSD found in this study was consistent with that reported in a multidimensional meta-analysis of psychotherapy for PTSD in which they assessed the participant inclusion rate of those screened for participation.[27]

CONCLUSION

Although the published pharmacologic clinical trials for PTSD provide a solid base for the provision of evidence-based treatments for PTSD, their external validity is often

limited since they tend to exclude a majority of participants, particularly those seeking treatment. In contrast, psychotherapy trial results may be applied to most patients with PTSD in routine clinical practice, although further evidence may be desirable, particularly regarding individuals with comorbid PTSD and substance use disorders.

Future pharmacologic clinical trials should carefully consider the trade-offs between the application of each exclusion criterion and its impact on representativeness.[10,19] Specification a priori of the goals of the study, better justification for each exclusion criterion, and estimation of the proportion of individuals ineligible for the trial would assist study design. Although efficacy studies may benefit from relatively stringent eligibility criteria to maximize detection of drug-placebo differences, effectiveness studies could place a larger emphasis on the generalizability of their findings by imposing less stringent eligibility criteria. Developing integrated forms of pharmacotherapy and psychotherapy that simultaneously target commonly overlapping psychiatric disorders may yield more informative results for mental health care providers and research funding agencies.[41]

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