Lack of Generalizability of PTSD Treatment Trials:

The Recent Brexpiprazole-Sertraline Trials as an Example

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Abstract

Background: Two recent studies demonstrated that brexpiprazole combined with sertraline was effective in reducing posttraumatic stress disorder (PTSD) symptoms, and an application has been submitted to the FDA for the combination treatment. When reading the inclusion and exclusion criteria of these studies, we suspected that many patients that we treat in our clinical practice would not have been eligible for the studies establishing the efficacy of the brexpiprazole-sertraline combination. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we estimated how many patients with PTSD in our practice would have qualified for the brexpiprazole-sertraline trials.

Methods: The sample was derived from the 3,800 psychiatric outpatients evaluated with semistructured diagnostic interviews, 417 of whom met *DSM-IV* criteria for PTSD upon presentation. The clinical protocol of the brexpiprazole-sertraline study listed the exclusion criteria. There were 11 exclusion criteria related to the patients' trauma history or psychiatric condition, almost all of which we assessed and applied to the sample.

Results: Three exclusion criteria were met by the majority of the patients: current major depressive disorder, PTSD age of onset before 16 years, and the interval between the onset of PTSD and patients' current age was 10 years or greater. Nearly 95% of patients met at least 1 of the exclusion criteria used in the brexpiprazole-sertraline studies.

Conclusions: While the effectiveness of the brexpiprazole-sertraline combination offers hope for addressing a significant unmet need in the treatment of PTSD, it is concerning that so few of our patients would have qualified for the clinical trials. As a result, we remain uncertain about the medications' effectiveness for most patients treated in clinical practice. We urge regulatory agencies to require industry to conduct studies that better reflect the patient populations seen in clinical practice.

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Posttraumatic stress disorder (PTSD) is a serious illness resulting in significant psychosocial impairment and excess mortality.[1–3] In the general population, the worldwide prevalence of PTSD is approximately 5%–6%, with prevalence estimates varying as a function of geographic region and exposure to various traumas.[4] Given its public health significance, there is a need for effective treatments of PTSD. Only 2 medications are Food and Drug Administration (FDA)–approved for the treatment of PTSD (sertraline, paroxetine), the last of which was approved more than 20 years ago in 2004. A recent Cochrane review of 66 placebo-controlled trials for PTSD supported the efficacy of selective serotonin reuptake inhibitors as first-line agents but noted that there remains an unmet need for other effective agents.[5]

A decade ago, Franco and colleagues[6] examined the generalizability of pharmacotherapy and psychotherapy trials for PTSD. They applied the most commonly used inclusion and exclusion criteria of these trials to respondents in the 2004–2005 National Epidemiologic Survey on Alcohol and Related Conditions who met criteria for PTSD in the past year. They estimated that three-quarters of the subsample who received psychiatric treatment in the past year would not have qualified for a pharmacotherapy treatment trial, and they therefore raised concerns about the generalizability of medication trials to patients seen in routine clinical practice. They noted that a limitation of their analysis was that the treatment received by the participants was not necessarily for PTSD, as the treatment variable encompassed treatment for any psychiatric disorder.

Clinical Points

- In an outpatient psychiatry sample, nearly 95% of patients who want treatment for PTSD would not have qualified for the brexpiprazole-sertraline trials.
- The most frequent reasons for exclusion were comorbid major depressive disorder, PTSD onset before age 16, and PTSD onset over 10 years prior to study.
- To ensure that clinical trial results are applicable to routine care, we urge regulatory agencies to require broader inclusion criteria in trials or enforce stricter accuracy in product labeling related to the generalizability of the samples included in registration trials.

Recently, 2 studies have demonstrated that brexpiprazole in combination with sertraline is effective in reducing PTSD symptoms,[7,8] and an application was submitted to the FDA for the combination treatment. If regulatory approval is granted, this combination would represent the first new pharmacologic treatment for PTSD in over two decades. When reading the inclusion and exclusion criteria of these studies, we suspected that the vast majority of the patients that we treat in our clinical practice would not have been eligible for the studies establishing the efficacy of the brexpiprazole-sertraline combination.

In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we administered a semistructured interview to evaluate the clinical profile of a large cohort of individuals who presented for treatment at our outpatient psychiatric practice. Based on each patient's clinical profile, we sought to determine how many patients with PTSD in our practice would have qualified for the brexpiprazole-sertraline trials. If the percentage is very low, this would raise questions about the approval of a medication combination that was not tested on most patients who will have it prescribed.

METHODS

The Rhode Island MIDAS project represents an integration of research methodology into a community-based outpatient practice affiliated with an academic medical center and has been described previously.[9] The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed, written consent.

The sample examined in the present report was derived from the 3,800 psychiatric outpatients evaluated with semistructured diagnostic interviews between December 1995 and June 2013, 417 of whom met *DSM-IV* criteria for PTSD upon presentation. The patients were interviewed by a diagnostic rater who administered the Structured Clinical Interview for *DSM-IV* (SCID)[10] and the borderline personality disorder section of the Structured Interview for *DSM-IV* Personality.[11] The interview also included items from the Schedule for Affective Disorders and Schizophrenia (SADS)[12] assessing suicidal ideation at the time of the evaluation and a history of suicide attempts. Consistent with our prior study on the generalizability of antidepressant efficacy trials, we defined clinically significant suicidal ideation as a score of 4 or more on the SADS item, indicating that the suicidal thoughts were severe, extreme, or very extreme.[13]

The diagnostic raters were highly trained and monitored throughout the project to minimize rater drift, as has been described in prior reports from the MIDAS project.[9] Reliability was examined in 65 patients using an observer-rater design. For disorders diagnosed in at least 2 patients by at least 1 of the 2 raters, the kappa coefficients were as follows: major depressive disorder (MDD) ($k = 0.90$), dysthymic disorder ($k = 0.88$), bipolar disorder ($k = 0.75$), panic disorder ($k = 0.95$), social phobia ($k = 0.84$), obsessive compulsive disorder ($k = 1.0$), specific phobia ($k = 0.93$), generalized anxiety disorder ($k = 0.85$), PTSD ($k = 0.87$), alcohol abuse/dependence ($k = 0.64$), drug abuse/dependence ($k = 0.64$), any somatoform disorder ($k = 1.0$), and borderline personality disorder ($k = 1.0$).

At the end of each SCID module, we added the following question about the reason for seeking treatment: "Are (symptoms of current disorder) a reason for coming for treatment now?" When asking this question, the interviewer reviewed the features of the disorder that had just been described so the patient understood to what the question referred. We followed the *DSM-IV* convention to distinguish between principal and additional diagnoses.[14] That is, the principal diagnosis referred to the disorder that the patient indicated was the main reason for seeking treatment; all other diagnoses were considered additional diagnoses.

The text of the brexpiprazole-sertraline papers provides an abbreviated list of the inclusion and exclusion criteria used to select subjects into the treatment trials.[7,8] However, the clinical protocol of the study (included as a supplement[7]) specifies each of the 30 exclusion criteria. There were 11 exclusion criteria related to the patients' trauma history or psychiatric condition, almost all of which we assessed and included in our database. Specifically, we recorded the following: age of onset of PTSD, which allowed us to determine if the index traumatic event occurred before age 16 and if PTSD developed more than 9 years before the evaluation; comorbid substance use disorders; whether a current anxiety disorder was the primary focus of treatment; severity of current suicidal ideation; suicidal behavior in the past year; and current psychotic disorder, MDD, bipolar disorder, borderline personality disorder, and

eating disorders (anorexia and bulimia nervosa). Our definition of drug and alcohol use disorder was narrower than the one used in the brexpiprazole-sertraline studies insofar as we only excluded individuals meeting the *DSM-IV* alcohol or substance dependence criteria (other than nicotine dependence), whereas the brexpiprazole-sertraline studies excluded individuals meeting the *DSM-5* alcohol or substance use disorder criteria. Also, in the brexpiprazole-sertraline studies, a minimum severity score was required on the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5), whereas we did not exclude patients based on PTSD symptom severity.

RESULTS

Patients

Just over 10% of the 3,800 patients in the sample met the full criteria for PTSD at the time of evaluation (n = 417, 11.0%). Among these 417 patients, 109 (26.1%) were diagnosed with PTSD as their primary disorder, while 308 (73.9%) had PTSD as a secondary diagnosis, of whom 264 (85.7%) expressed a desire for treatment for those symptoms. The focus of the present study is the 373 (109 + 264) patients wanting treatment for PTSD.

The group included 101 (27.1%) men and 272 (72.9%) women who were a mean age of 36.4 years (SD = 11.5). At the time of the evaluation, approximately one-third of the subjects were either married (32.4%) or never married (34.3%); the remainder were divorced (17.4%), separated (6.2%), widowed (1.6%), or living with someone as if in a marital relationship (8.0%). A minority of the sample did not graduate high school (12.9%). More than one-sixth (18.0%) graduated from college. The racial composition of the sample was 79.9% white, 6.4% black, 5.6% Hispanic, 0.3% Asian, and 7.8% from another or a combination of the above racial backgrounds. The most common index traumas in the patients were sexual assault by a family member (34.3%), nonsexual assault by a family member or someone they knew (29.0%), witnessing the death or violent assault of another person (10.7%), serious accident or fire (7.2%), and sexual assault by a stranger (4.3%).

Number of Psychiatric Outpatients with PTSD Meeting Exclusion Criteria Used in the Brexpiprazole-Sertraline Studies

Three exclusion criteria were met by the majority of the patients: current MDD, PTSD age of onset before age 16, and the interval between the onset of PTSD and patients' current age was 10 years or greater (Table 1). One other criterion was present in more than a quarter of the sample—comorbid borderline personality disorder. All but 25 of the 373 patients met at least 1 of the exclusion criteria. That is, 93.3% of patients met at least 1 of the exclusion criteria.

Table 1.

Percentage of Patients Who Would Have Met Different Psychiatric Exclusion Criteria in the Brexpiprazole-Sertraline Trials

Exclusion criterion	Patients meeting criterion, % (n)
Current major depressive disorder	63.8% (238)
Principal anxiety disorder	5.9% (22)
Borderline personality disorder	26.8% (100)
Age of onset of PTSD before 16 y	52.5% (196)
PTSD onset 10 or more years before current age	60.9% (227)
Significant suicidal ideation	8.9% (37)
Suicide attempt within past year	12.3% (46)
Current bipolar disorder	11.3% (42)
Current drug or alcohol dependence	8.3% (31)
Current anorexia or bulimia	1.3% (5)
Age greater than 65 y	0.8% (3)
Current psychotic disorder	2.4% (9)
Current binge eating disorder	3.5% (13)
Met at least 1 of the above exclusion criteria	93.3% (348)

We repeated these analyses after including the 109 patients who had PTSD as a secondary disorder but who did not indicate that they wanted their treatment to address the PTSD. The results were nearly identical—93.8% (n = 391) of the 417 patients with PTSD met 1 or more of the exclusion criteria.

The studies by Davis et al[7] and Hobart et al[8] differed in the cutoff for excluding patients based on how long ago the index trauma occurred. We initially analyzed the data based on the Davis et al[7] definition, in which patients were excluded if the index trauma occurred 10 or more years before the study. In the subsequent publication by Hobart et al, the definition was narrowed to exclude patients only if the index trauma occurred more than 15 years before screening. Narrowing the exclusion had a clear impact on the number who would be excluded due to this criterion. The number of patients whose index trauma occurred more than 15 years before presenting to treatment was 193, 34 less than 227 excluded based on the 10 or more years definition of the criterion. However, when we reanalyzed the data accounting for all the exclusion criteria for the sample of 373 patients wanting treatment for PTSD, then only an additional 4 patients would be excluded when the narrower definition of the criterion was used (total excluded 92.2%).

DISCUSSION

A small minority of the patients in our clinical practice who were diagnosed with PTSD would have qualified for the brexpiprazole-sertraline studies. Nearly

95% of the patients would have been excluded due to failure to meet one or more of the psychiatric exclusion criteria. If anything, our estimate may be low because we did not assess several exclusion criteria that were used in the studies (eg, subjects receiving disability payments for a psychiatric disorder, subjects engaged in compensation litigation, medical exclusions), we defined some exclusion criteria more narrowly than the studies' protocols (eg, current *DSM-IV* drug or alcohol dependence rather than *DSM-5* drug or alcohol use disorder), and we did not require a minimum score on the CAPS-5. In short, the vast majority of patients who presented to a general, psychiatric outpatient practice who were diagnosed with PTSD and wanted treatment for it were not represented in the trials establishing the efficacy of the brexpiprazole-sertraline combination.

Before conducting our analyses, we faced the decision of which patients diagnosed with PTSD should be included. In general population epidemiological studies, no distinction is made between principal and secondary diagnoses because patients are not presenting for treatment. However, the diagnostic evaluation in the present study was conducted when patients began treatment. We thought it inappropriate to include patients with PTSD as a secondary diagnosis who did not want treatment for PTSD because we approached the analyses from a clinical perspective, and we considered this group as less relevant because medication would likely not be prescribed for PTSD in such cases. The question, then, was whether to include the patients who wanted treatment for PTSD as a secondary diagnosis. We, a priori, decided to include these patients because when the medication is approved, it will likely be prescribed to individuals who want treatment for their PTSD whether the PTSD is the primary or a secondary disorder.

There are several limitations to the present analysis. This was a single-site study, and any single-site study should be replicated in other samples with different demographic and clinical characteristics. For example, the most common index trauma in the patients was sexual assault by a family member, which was experienced by approximately one-third of the patients. A relatively high rate of childhood sexual abuse would account for the high number of exclusions for those patients with an age of onset before 16 years and onset of the disorder more than 10 years ago. Childhood sexual or physical abuse could not have been the index trauma in the brexpiprazole-sertraline studies. However, an FDA indication for the brexpiprazole-sertraline combination was sought for PTSD in general and not for PTSD unrelated to childhood abuse.

We did not assess many of the exclusion criteria used in the brexpiprazole-sertraline studies. We did not evaluate any of the medical exclusion criteria and some of the clinical criteria. Thus, our estimate of the percentage of patients in our clinical sample who would not have qualified for the study may be an underestimate. Also, some of our assessments did not exactly correspond to the assessments in the clinical trials. For example, we required a score of 4 or greater on the SADS suicidal ideation item. A rating of 4 on this item indicates that the patient "often thinks of suicide and has thought of or mentally rehearses a specific plan or has made a suicidal gesture of a communicative rather than potentially medically harmful type." A rating of 5 indicates the patient has made preparations for a potentially serious suicide attempt, and a rating of 6 indicates that a suicide attempt was made. In the brexpiprazole-sertraline studies, patients were excluded if they were positive on items 4 or 5 of the Columbia-Suicide Severity Rating Scale, indicating the presence of suicidal intent. While there is a lack of perfect correspondence between the assessments of current suicidality, there is significant overlap. Moreover, recent suicidal ideation was not, in fact, a frequent reason for exclusion in our sample, and it rarely occurred in the absence of another exclusion criterion.

A further distinction between our study and the brexpiprazole-sertraline trials is that diagnostic assessments in the present study were conducted using *DSM-IV* criteria, whereas those trials employed *DSM-5* criteria. The potential impact of this change in diagnostic framework on the results is uncertain.

The presence of current MDD was the most frequent reason that patients in our clinical practice would not have qualified for the PTSD trials. Other clinical trials for PTSD have found high rates of current depression in their samples.[15,16] A review of the comorbidity between PTSD and MDD, which combined the results of studies of both patient and nonpatient samples, found that slightly more than half of individuals with PTSD were also diagnosed with MDD.[17] However, while the brexpiprazole-sertraline studies excluded subjects with current MDD, this did not exclude subjects reporting depressive symptoms of mild-moderate severity on a self-report scale.

For years, researchers have questioned how well findings from clinical trials apply to patients seen in everyday clinical practice. To address this, some studies have compared trial participants recruited through advertisements ("symptomatic volunteers") with those referred from clinical settings, examining their demographic, clinical, and treatment response profiles. In a PTSD trial for women with co-occurring substance use disorder, participants recruited via advertisements had higher baseline PTSD severity and more drug-use days than clinic-referred, treatment-seeking patients.[18] Recruitment source also moderated treatment effects in this study. Beyond PTSD, a comparison of symptomatic volunteers to clinic patients with anxiety disorders found systematic differences in demographic characteristics, prior treatment exposure, symptom counts, and

treatment expectations.[19] By contrast, studies of depressed patients have found that symptomatic volunteers and clinic-referred patients are more alike than different, thereby supporting the view that efficacy trial results are broadly generalizable to patients seeking treatment.[20–24] It is not clear how many of the patients in the brexpiprazole-sertraline studies were clinic-referred versus symptomatic volunteers, though more than 40% of the subjects in the studies had never received prior treatment for PTSD. While there is some inconsistency in the literature regarding the comparability of symptomatic volunteers to clinic-referred patients, the issue addressed in the present study is how many patients in a clinical sample would have failed to qualify for the brexpiprazole-sertraline studies based on the inclusion/exclusion criteria.

The present study focused on the 2 recently published studies of brexpiprazole-sertraline, whereas the title of the paper casts a broad net and raises the question about the overall generalizability of PTSD trials. While it is beyond the scope of the present paper to comprehensively review the inclusion/exclusion criteria of all PTSD trials, it is important to recognize that PTSD trials have varied in their methodology. For example, in some placebo-controlled studies for PTSD, patients with depression were not excluded[15,16,25–31] nor were patients excluded whose PTSD onset more than 10 years before the evaluation[15,16,25–31]—the two most frequent reasons that patients in our clinical sample would have been excluded from the brexpiprazole-sertraline studies. Our goal in choosing a broad title was to bring attention to this issue and perhaps stimulate further research and discussion regarding the variability and appropriateness of inclusion/exclusion criteria in PTSD clinical trials.

Exclusion criteria in registration trials of medications for psychiatric disorders encompass several domains, such as comorbid medical and psychiatric disorders, substance use, and insufficient severity of the target condition. Sometimes it is obvious why certain exclusion criteria are used; sometimes an explanation and justification are warranted. In the brexpiprazole-sertraline trials, some of the exclusion criteria were specific to PTSD, such as the age at which the index trauma occurred and the duration of the PTSD symptoms. The authors did not provide a reason for these exclusions. Because these exclusion criteria were among the most frequent grounds for patients in our outpatient sample to have been excluded from the clinical trial, it is important to understand the rationale for these exclusions.

While clinical trials of PTSD vary in their inclusion/exclusion criteria, it is notable that reviews and meta-analyses of the pharmacotherapy of PTSD have neglected to discuss the impact of inclusion/exclusion criteria on the generalizability of the studies to patients treated in clinical practice.[32–37]

The present findings extend the study of Franco et al,[6] who applied the exclusion criteria commonly used in pharmacotherapy trials for PTSD to general population subjects who met PTSD criteria within the past 12 months and who had sought psychiatric treatment during the same time period. There are some notable differences in the methods of that study and the present one. They did not assess 2 of the most common reasons that resulted in exclusion in the present sample (PTSD age of onset less than age 16, PTSD onset more than 10 years before the patient's current age), and they also did not assess borderline personality disorder. On the other hand, Franco et al[6] applied a medical exclusion criterion, whereas we did not.

An important question is whether findings from studies like the present one should influence regulatory decisions. One could argue that the primary aim of placebo-controlled trials is to demonstrate a medication's effectiveness and safety, rather than establishing its efficacy for all, or most, potential patients who might have the medication prescribed. However, if the inclusion and exclusion criteria of phase 3 registration trials exclude the vast majority of patients for whom the medication is indicated, it raises important questions about the approval process and/or product labeling.

If generalizability is to be considered in regulatory decisions, a challenge lies in determining how to operationalize it. Even before nominating a minimum percentage of patients in routine clinical care who should qualify for a trial, a key issue is how to validly assess generalizability. The MIDAS project is unique in that it integrates research assessment methodology into routine clinical practice, thus providing a more systematic and comprehensive evaluation of comorbid conditions compared to diagnostic assessments based on unstructured clinical interviews that are the norm in clinical settings.[38–40] However, the MIDAS project is conducted in a single practice that does not encompass the diversity of clinical settings. Most patients in our practice are white and have health insurance; thus, our findings must be replicated in other clinical samples with different sociodemographic characteristics. On the other hand, the previous study from the MIDAS project questioning the generalizability of antidepressant efficacy trials (AETs),[13] which revealed that most depressed outpatients receiving treatment in clinical practice would not qualify for an AET, was later replicated multiple times, including an analysis from the multisite Sequenced Treatment Alternatives to Relieve Depression trial.[41–43]

Perhaps the best way to assess generalizability is a modification of the approach taken by Franco and colleagues[6]—apply the specific exclusion criteria used in a treatment study to a representative sample of the general population with the index condition. Hoertel and colleagues proposed something similar.[44] Assuming the

databases exist to construct an index of generalizability (IOG), what minimum IOG should be required for drug approval? To be sure, any numerical value is somewhat arbitrary in the same way that a *P* level of .05 has been adopted to indicate statistical significance and a number needed to treat of 10 to indicate clinically beneficial treatment. Requiring the reporting of an IOG in clinical trials will likely raise clinicians' awareness of the gap between research and clinical practice. Whatever IOG the field settles on, we believe it should be higher than 5%.

An easier-to-implement alternative to requiring a minimum IOG to attain regulatory approval is the enforcement of the FDA's guidance in product labelling. The FDA's industry guidance monograph on the labeling of prescription drugs provides guidelines for the content and format of a product's package insert. The Clinical Studies section of a product's label is intended to identify the important limitations of the empirical evidence supporting a product's efficacy.[45] Specifically, the FDA's guideline states that a label's description of the study population "should identify those characteristics that are important for understanding how to interpret and apply the study results. The description should identify important inclusion and exclusion criteria." If the brexpiprazole-sertraline combination receives FDA approval, it would be easy enough for the product label to identify key exclusion criteria that limit generalizability such as the presence of comorbid MDD or childhood onset of PTSD.

We do not believe that industry will modify its approach toward seeking regulatory approval based on studies of the type reported herein unless regulatory agencies require them to do so. As evidence that industry is unlikely to change its approach, after the studies raising concerns about the generalizability of AETs were published, and replicated, the inclusion/exclusion criteria for AETs actually narrowed even further, thereby suggesting that AETs may have become even less generalizable than they had been previously.[46]

When prescribing any medication, it is essential to weigh the potential benefits against the possible harms. Second-generation antipsychotics such as brexpiprazole can cause clinically significant adverse effects. For patients to make informed decisions about the risks and benefits of medication, it is crucial to determine whether medication has been tested on individuals similar to them. It would be concerning if nearly 95% of patients with the condition for which the medication is approved would not have qualified for the clinical trial. This recommendation is not specific to PTSD and pertains to the evaluation of treatments for all psychiatric disorders.

In conclusion, while the effectiveness of the brexpiprazole-sertraline combination may offer hope for addressing the significant unmet need in PTSD treatment, it is troubling that so few of the patients in our practice would have qualified for the clinical trials. As a result, we remain uncertain about its effectiveness for the individuals we treat. We urge regulatory agencies to require industry to conduct studies that better reflect the patient populations seen in clinical practice, or to enforce their own guidelines regarding product labelling.

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