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Research paper

Variability in the substance use disorder exclusion criterion in antidepressant efficacy trials

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ABSTRACT

Background: Substance use disorders are the most commonly excluded psychiatric disorder in antidepressant efficacy trials (AETs). In a recent review of AETs we noticed variability in the definition of the substance use disorder exclusion criterion. In the present report we examined in greater detail the variability in defining the substance use disorder exclusion criterion, the potential impact of this variability on excluding patients from an AET, and whether the definition of the criterion has changed in the past 20 years.
Methods: We identified 170 AETs published during the past 20 years and compared the studies published during the past 5 years (n=56) to the studies published during the 15 prior years (n=114).
Results: Substance abuse was more frequently used as an exclusion criterion than substance dependence. Six time frames have been used as the basis of exclusion, the most frequent being the past 12 months. The time frame had a greater impact on the number of patients who would be excluded than the abuse/dependence distinction. The definition of the substance use exclusion criterion was no different in the studies of the past 5 years compared to the prior 15 years.
Limitations: A limitation of the present analysis is that it was based on published placebo-controlled studies of antidepressants.
Conclusion: Studies varied in whether abuse or dependence was the basis of exclusion, whether alcohol or illicit drugs or both were the basis of exclusion, and the time frame of the disorders' presence. We raise the question of whether the routine exclusion of patients with a substance use disorder should be reflected in a product's label.

1. Introduction

Concerns about the generalizability of antidepressant efficacy trials (AETs) have been raised for many years. More than a decade ago our clinical research group found that the majority of patients with major depressive disorder (MDD) presenting for treatment to our outpatient practice would have likely been excluded from an AET because they did not meet the study's inclusion/exclusion criteria (Zimmerman et al., 2002). This finding was independently replicated multiple times (van der Lem et al., 2011; Wisniewski et al., 2009; Zetin and Hoepner, 2007). In our initial review of the exclusion criteria used in AETs, we found that alcohol and drug abuse/dependence was the most commonly excluded comorbid psychiatric disorder (Zimmerman et al., 2004).

We recently updated and expanded our initial review to 170 placebo-controlled AETs published over the past 20 years and found that substance use disorder remains the most commonly excluded psychiatric disorder (Zimmerman et al., 2015). In conducting this review we found variability among studies in whether patients were excluded due a history of drug or alcohol abuse, dependence, or either, and variability in the time period during which the patients could not have had substance use problems (e.g., current, past year, lifetime). In the present report we examined in greater detail the variability in defining the substance use disorder exclusion criterion, the potential impact of this variability on excluding patients from an AET, and whether the definition of the criterion has changed in the past 20 years.

2. Methods

To ascertain the sample of studies of AETs, we first reviewed the Tables of Contents of 49 journals from January 1995 through

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December 2014. The journals reviewed were those that had published studies included in prior comprehensive reviews of placebo-controlled AETs (Papakostas and Fava, 2009; Undurraga and Baldessarini, 2012). This was supplemented with a search of the Medline (via PubMed), Embase (via ovid), and Psychinfo (via Ebsco host) databases for the same time period. We used the search terms "depression" or "depressive" and "placebo". Only articles published in English were included. We also examined the reference lists of meta-analyses of AETs, and the studies identified from our literature review.

We did not include trials that focused on refractory depression, chronic depression, bipolar, psychotic, atypical or melancholic subtypes of depression, trials focused on depressed patients with particular symptoms such as anxious features, trials based on inpatient samples, or trials limited to patients with a particular comorbid condition such as alcoholism, anxiety disorder, or medical illness. We excluded these studies from our review because, by definition, they focused on limited groups of depressed patients and this would have biased the findings of the larger project which examined the overall generalizability of AETs (Zimmerman et al., 2015).

We only included trials focused on patients with major depression, and therefore did not include trials that were based on an admixture of patients with major depression, dysthymic disorder, and minor depression. The inclusion of a small number of patients with bipolar depression was not the basis for excluding the trial from our review, though trials limited to patients with bipolar disorder were not included. Trials resulting in multiple publications based on the same sample (and the same set of inclusion/exclusion criteria) were included only once. We did not include trials of intravenous or injectable forms of medication, and also did not include trials of medication combination or augmentation strategies. We included trials whether or not the medication has received regulatory approval for the treatment of depression.

Two of the authors independently reviewed each article and completed a form listing the psychiatric inclusion and exclusion criteria used in the study. The reliability for determining whether an alcohol use disorder (alcohol abuse, k=.95; alcohol dependence, k=.95) or drug use disorder (drug abuse, k=.93; drug dependence, k=.93) was used as an exclusion was very high. After comparing the results of their data abstraction the reviewers resolved discrepancies. Most studies that excluded patients with an alcohol or drug use disorder were explicit in their description, and denoted abuse and/or dependence as the basis of exclusion and distinguished between alcohol and drug use disorders. However, some studies excluded patients with substance use disorders without further specification. It was therefore unclear if "substance use disorders" referred to drugs of abuse only or whether it also included alcohol use disorders. Some studies excluded patients with any comorbid psychiatric disorder or any comorbid Axis I disorder without specifically noting that patients with substance use disorders were excluded. It was uncertain if substance use disorders fell under the any Axis I disorder rubric. In our analysis we describe the frequencies of each of these occurrences. Sometimes the exclusion did not refer to DSM-IV diagnostic categories of abuse and dependence. We equated "alcohol addiction" and "alcoholism" to alcohol dependence, and "excessive drinking habits" to alcohol abuse.

2.1. Data analyses

We identified 170 AETs published during the past 20 years. Table 1 lists the 15 medications that were studied in at least 5 trials. We compared the studies published during the past 5 years (2010–2104, n=56) to the studies published during the 15 prior years (n=114). The groups were compared by the chi-square statistic, or by Fisher's Exact Test if the expected value in any cell of a 2×2 table was less than 5.

Table 1
Medications studied in 170 placebo-controlled antidepressant efficacy trials.[a]

Medication	Number of studies
Agomelatine	7
Aprepitant	5
Bupropion[b]	9
Citalopram	7
Desvenlafaxine	14
Duloxetine	25
Escitalopram	12
Fluoxetine	16
Hypericum	11
Levomilnacepran	5
Paroxetine[c]	22
Quetiapine-XR	5
Sertraline	9
Venlafaxine[d]	12
Vortioxetine	9

[a] Only medications studied in at least 5 studies are included in the table.
[b] Includes 4 studies of bupropion SR and 5 studies of bupropion-XL.
[c] Includes 16 studies of paroxetine and 5 studies of paroxetine-CR.
[d] Includes 4 studies of venlafaxine and 8 studies of venlafaxine-XR.

3. Results

Approximately two-fifths (38.2%, n=65) of the 170 studies explicitly excluded patients with a history of an alcohol use disorder. Of the remaining 105 studies, 61 indicated that they excluded patients with a substance use disorder and another 10 studies excluded patients with any comorbid Axis I disorder. We interpreted these exclusions as indicating that patients with an alcohol use disorder would be excluded from the study; thus, the vast majority (80.0%, n=136) of the 170 AETs excluded patients with an alcohol use disorder (Table 2). Alcohol abuse was more frequently used as an exclusion criterion than alcohol dependence. Six time frames have been used as the basis of exclusion, the most frequent being the past 12 months. The use of an alcohol use disorder exclusion was not more frequent in the studies of the past 5 years compared to the prior 15 years (80.4% vs. 79.8%, $X^2=0.01$, n.s.).

Approximately one-sixth (16.5%, n=28) of the 170 studies explicitly excluded patients with a history of a drug use disorder. Of the remaining 142 studies, 97 indicated that they excluded patients with a substance use disorder and another 10 excluded patients with any comorbid Axis I disorder. We again interpreted these exclusions as indicating that patients with a drug use disorder would be excluded from the study; thus, the vast majority (79.4%, n=135) of the 170 AETs excluded patients with a drug use disorder (Table 3). Drug abuse was more frequently used as an exclusion criterion than drug dependence. Six time frames have been used as the basis of exclusion, the most frequent being the past 12 months. The use of a drug use disorder exclusion was not more frequent in the studies of the past 5 years compared to the prior 15 years (80.4% vs. 78.9%, $X^2=0.05$, n.s.).

What impact might different definitions of the alcohol and drug use disorder exclusions have on the number of patients who would be excluded from an AET? We examined the percentage of depressed outpatients seen in our practice as part of the Rhode