

Abstract

Bipolar disorder (BD) is a major depressive mental health disorder with frequent and extreme mood fluctuations. Numerous mental health disorders and behavioral abnormalities, including suicidal ideologies, are associated with BD due to its volatility. This study analyzed the relationship between BD and comorbid mental health disorders in clinical trials to better understand their respective frequency and inclusion in regulated settings. Overall, researchers found 2808 mental health terms within the inclusion and exclusion criteria of BD clinical trials, of which 956 (34.05%) were included in such trials. Suicide-related terms yielded the most disproportionate inclusion with 370 total terms which were excluded from BD clinical trials 92.97% of the time. These data indicate a need for a more proportional inclusion of comorbid mental health disorders in BD clinical trials with a key emphasis on suicide-related concerns. An increase in comprehensive clinical trials could help reduce the risk of early mortality in a highly vulnerable population.

Background

Bipolar disorder (BD) is a major depressive mental health disorder known for volatile mood fluctuations. Due to the frequent and extreme mood changes, BD is often associated with comorbid mental health conditions and abnormal thoughts including suicidal ideations which can hinder psychosocial recovery for BD treatment (Bennett et al., 2019, 1-9). The suicide rate is roughly 20-30 times higher among individuals with BD which is the highest rate of all psychiatric conditions (Miller & Black, 2020, 1-10). Medications such as lithium have shown some merit in reducing suicide rates in the general population, however, that success appears to be limited in the prevention of recurrent suicide attempts in those with BD (Katz et al., 2022, 24-32). Interestingly, intravenous ketamine has yielded improvements in depressive symptoms, anxiety, and suicidal tendencies in BD patients (McIntyre et al., 2020, 903-910). It's clear that BD is associated with concomitant mental health concerns that potentially limit BD treatment efficacy and increase the risk of early mortality, exemplifying the need for additional research in this vulnerable group.

Methods

To determine the proportional relationship between bipolar disorder and coexisting mental health disorders in clinical trials, this study investigated the historical presence of secondary mental health conditions within the inclusion and exclusion criteria of clinical trials. Researchers used data from all interventional clinical trial study reports published from 1990 to 2022 using MeSHID XXXXXXXXXX that identified mental health terms in both the inclusion and exclusion criteria. Frequencies of search terms were tallied within the inclusion and exclusion criteria of each BD study. Counts of term mentions per study eligibility section were converted to binary data so that each search term (or a synonymous term) was counted once per study in either the inclusion or exclusion criteria. Any clinical trials that lacked explicit inclusion and exclusion sections and those that mentioned the same search term in both sections were flagged and

manually curated to ensure the correct term assignment. The resulting datasets were organized using the tidyverse (1.3.2) in R (4.2.2) and Microsoft Excel was used to generate the tables. Figures were created using BioVenn (1.1.3) and ggplot2 (3.4.0) in R. A secondary statistical analysis was conducted using the r 'stats' package 'aov' ANOVA function.¹

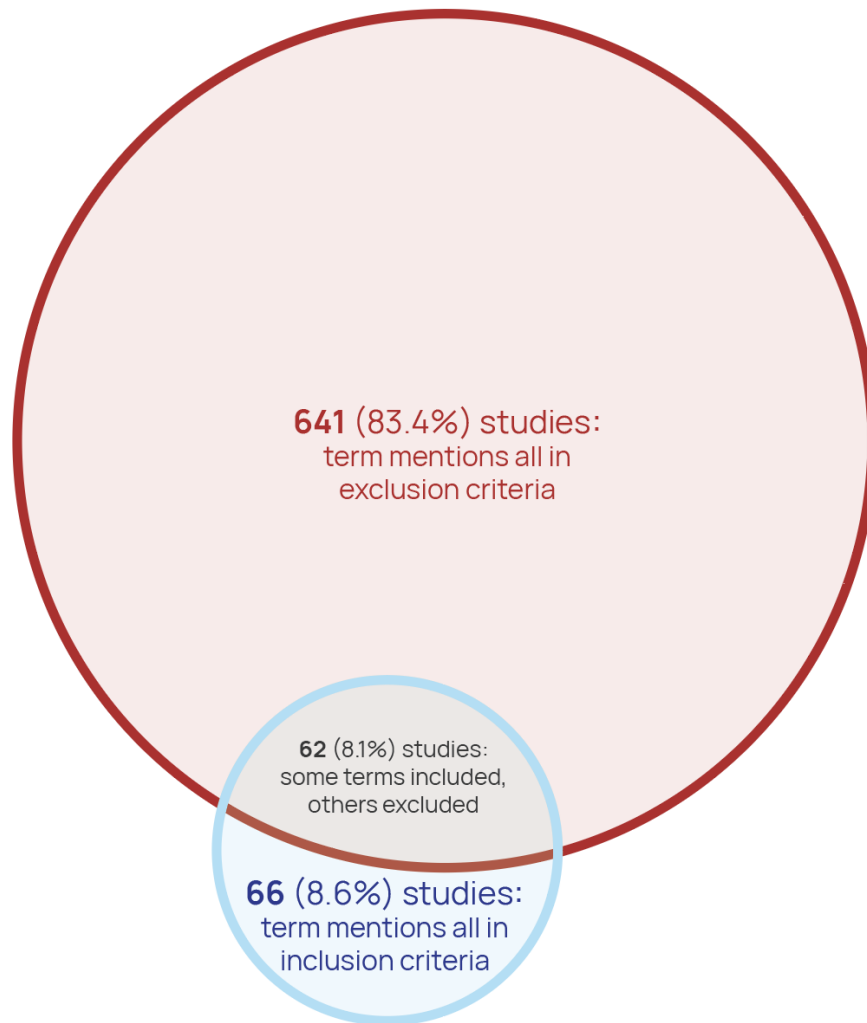


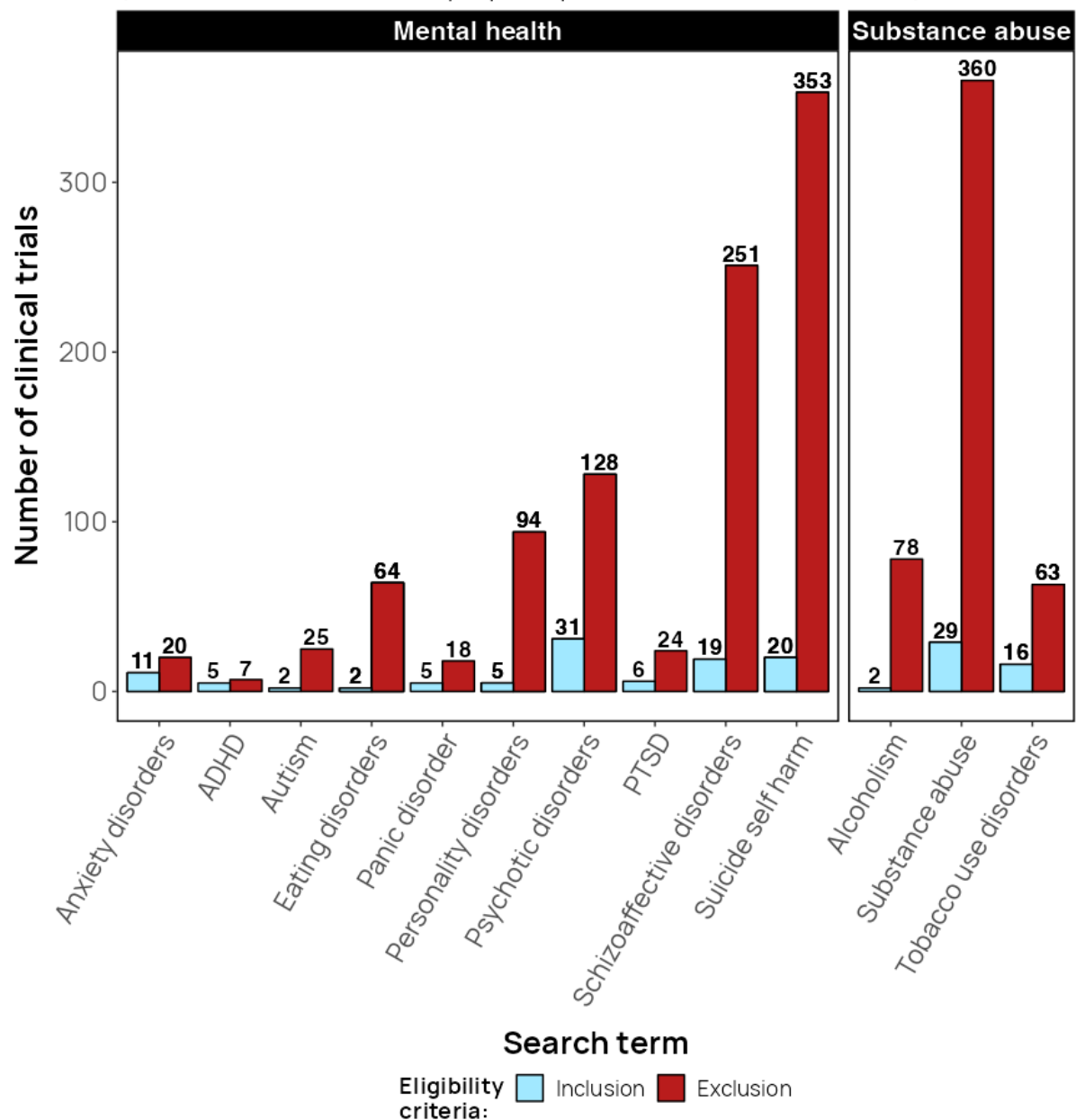
Figure 1. Proportional Venn diagram showing the number of bipolar disorder clinical trial study reports that exclusively excluded mental health-related search terms, exclusively included these terms, and those that excluded some and excluded others.

Table 1. Inclusion and exclusion frequencies of the mental health terms and the respective inclusion rates in BD clinical trials.

Search Term	Inclusion criteria	Exclusion criteria	Term groups
Alcoholism	2	78	Alcoholism
Anxiety disorders	5	11	Anxiety disorders
Generalized anxiety disorder	6	9	
Attention deficit hyperactivity disorder (ADHD)	5	7	ADHD
Autism	2	25	Autism
Panic disorder	5	18	Panic disorder
Borderline personality disorder	0	35	Personality disorders
Obsessive-Compulsive Disorder (OCD)	3	47	
Personality disorders	2	12	
Psychosis	24	105	Psychotic disorders
Psychotic disorders	7	23	
Post-traumatic stress syndrome (PTSD)	6	24	PTSD
Schizoaffective disorders	3	5	Schizoaffective disorders
Schizophrenia	16	246	
Substance abuse	11	234	Substance abuse
Substance use	18	126	
Self injurious behavior	0	3	Suicide self harm
Suicidal ideation	7	105	
Suicide	13	245	
Smoking	9	15	Tobacco/nicotine use disorders
Tobacco use	1	7	
Tobacco/nicotine dependence	6	41	
Anorexia	0	30	Eating disorders
Binge eating disorder	1	0	
Bulimia	1	28	
Eating disorders	0	6	
TOTAL:	153(9.3%)	1485 (90.7%)	

Search Terms in Bipolar Disorder Clinical Trial Eligibility Criteria:

(Based on clinical trial study reports published from 1990 to 2022.)



(Source: www.clinicaltrials.gov)

Figure 2. Comparison of inclusion and exclusion frequencies of terms related to comorbid mental health and substance abuse disorders in bipolar disorder clinical trials.

Results and Discussion

Bipolar disorder (BD) is a major depressive mental health disorder that is commonly associated with comorbid mental health disorders and extreme mood fluctuations. Despite the severity of these conditions and the apparent tie to an increased suicide rate, researchers noted a disproportionate relationship between the inclusion and exclusion of comorbid mental health conditions in BD clinical trials. Researchers identified 1330 BD studies that included mental health-related search terms within the eligibility section. Of these studies, 128 studies included mental health-related terms within the eligibility section versus 703 studies excluding such terms, as shown in Figure 1. A total of 1573 instances of mental health terms were identified within the eligibility section of BD clinical trials and only 152 or 9.7% were included in BD clinical trials, a rate that was drastically magnified for some specific search terms. For example, suicide-related terms were identified 370 times and included in BD clinical trials just 20 times (5.4%). Additionally, “schizophrenia”, “substance abuse”, and “psychosis” were excluded 246, 234, and 105 times each, respectively. Based on these data, researchers established a significant difference between the inclusion and exclusion of mental health terms in BD clinical trials by ANOVA ($p = .00167^{**}$) and Pearson correlation ($p = .0008363$).

A historical tie between BD and comorbid mental health disorders exists and can be considered a contributor to the increased suicide rate among individuals with BD. Despite this relationship and the severe impact, clinical trials still fail to accept BD in comprehensive clinical trials. More specifically, BD clinical trials rarely include patients with a more severe prognosis, limiting the scope of the existing BD clinical trials research. Future BD clinical trials should more openly accept those with comorbid mental health disorders and those with more advanced stages of the disease to better understand the capacity for improvement in this vulnerable and volatile group.

References

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