

Abstract

Most commonly known for its unpredictable and extreme mood fluctuations, bipolar disorder (BD) is a major depressive mental health disorder with ties to chronic pain, accelerated aging, and rheumatic conditions like arthritis. Rheumatic conditions and chronic pain can exacerbate BD symptomatology whereas BD can accelerate aging while deteriorating brain function. This study reviewed the eligibility criteria of BD clinical trials to determine the proportional inclusion of rheumatology, aging, and pain-related search terms within such trials using ClinicalTrials.gov to determine if studies have effectively investigated co-treatment options and efficacy. The results, while limited, indicated a much greater exclusion (85.5%) of rheumatic conditions than inclusion (14.5%). Of all terms identified, "Aging" appeared the most frequently but established a slightly higher inclusion rate (20.45%) than the collective in BD clinical trials. Other search terms (IE Migraines) were identified much less frequently but maintained lower, sometimes trivial inclusion rates. This study highlights a need for increased consideration of rheumatic conditions, chronic pain, and age-related conditions (collectively RCPA) in BD clinical trials given the current exclusion rate and simultaneous shortage of such conditions within eligibility criteria.

Background

Bipolar disorder (BD) is a mental health disorder that is commonly perceived for its unpredictable and extreme mood fluctuations, including major depressive episodes. Correspondence exists between BD and rheumatic conditions. For example, rheumatoid arthritis increases the risk of BD which is believed to be related to chronic inflammation. RA pharmacotherapy with corticosteroids has also been implicated in BD symptom exacerbation. (Charoenngam et al., 2019, 112484). Rheumatoid arthritis chronic nature also increases the risk of anxiety and depression which could further exacerbate BD events (Marrie et al., 2018, 970). Despite the evidence linking rheumatic conditions and mood disorders like BD, treatment efficacy remains understudied and inconclusive for these coexisting conditions (Jones et al., 2020).

BD is also associated with accelerated aging due to numerous physiological abnormalities such as telomere length alterations, DNA methylation, mitochondrial DNA copy number, inflammation, and oxidative stress (Fries et al., 2020, 107). Brain function is believed to deteriorate at an expedited rate in BD patients if untreated, however, treatment with lithium has exhibited the potential to decrease biological brain age which may benefit those with BD or neurodegenerative disorders (Van Gestel et al., 2019, 1179). Migraines are considered the most common neurological comorbidity among those with BD which occur at a higher rate than the general population (McIntyre et al., 2022).

Like rheumatic conditions and accelerated aging, chronic pain disorders are considered common among BD patients but can simultaneously and independently increase the risk of suicide in this population (Vadukapuram et al., 2021). Pain treatment can be problematic for BD patients given the propensity of these individuals to abuse common pharmacologic agents such as opioids, benzodiazepines, and marijuana (Sutherland et al., 2018, 290).

Methods

This study collected and analyzed the eligibility criteria of BD clinical trials from 1990 to 2022 from ClinicalTrials.gov (MeSHID D001714). All RCPA terms found in the eligibility criteria were identified and tallied to collect the frequency of such terms throughout all BD clinical trials. Once collected, data were organized using the tidyverse (1.3.2) suite of R (4.2.2) packages. Each study was permitted one search term instance if a single study repeated a term within the inclusion or exclusion criteria section. A manual inspection was conducted to assign search terms to the appropriate inclusion or exclusion section when terms were ambiguous within a study's eligibility section. Data were analyzed using the R Stats package ('aov' function) to establish any significant trends. Figures were created using ggplot2 (3.4.0) in R. The respective inclusion and exclusion frequency of all collected search terms is provided in Table 1 while the proportional inclusion and exclusion frequencies of the most notable search terms are represented in Figure 1.

Table 1. Inclusion and exclusion frequencies of RCPA-related search terms in bipolar disorder clinical trials.

Search term	Inclusion frequency	Exclusion frequency
Aging	9	35
Arthritis	1	6
Rheumatoid arthritis	0	3
Chronic pain	1	6
Fibromyalgia	0	5
Musculoskeletal pain	1	0
Myalgia	0	4

Migraines	0	12
TOTAL:	12 (14.5%)	71 (85.5%)

Search Terms in Bipolar Disorder Clinical Trial Eligibility Criteria:
(Based on interventional trials initiated between 1990 and 2022.)

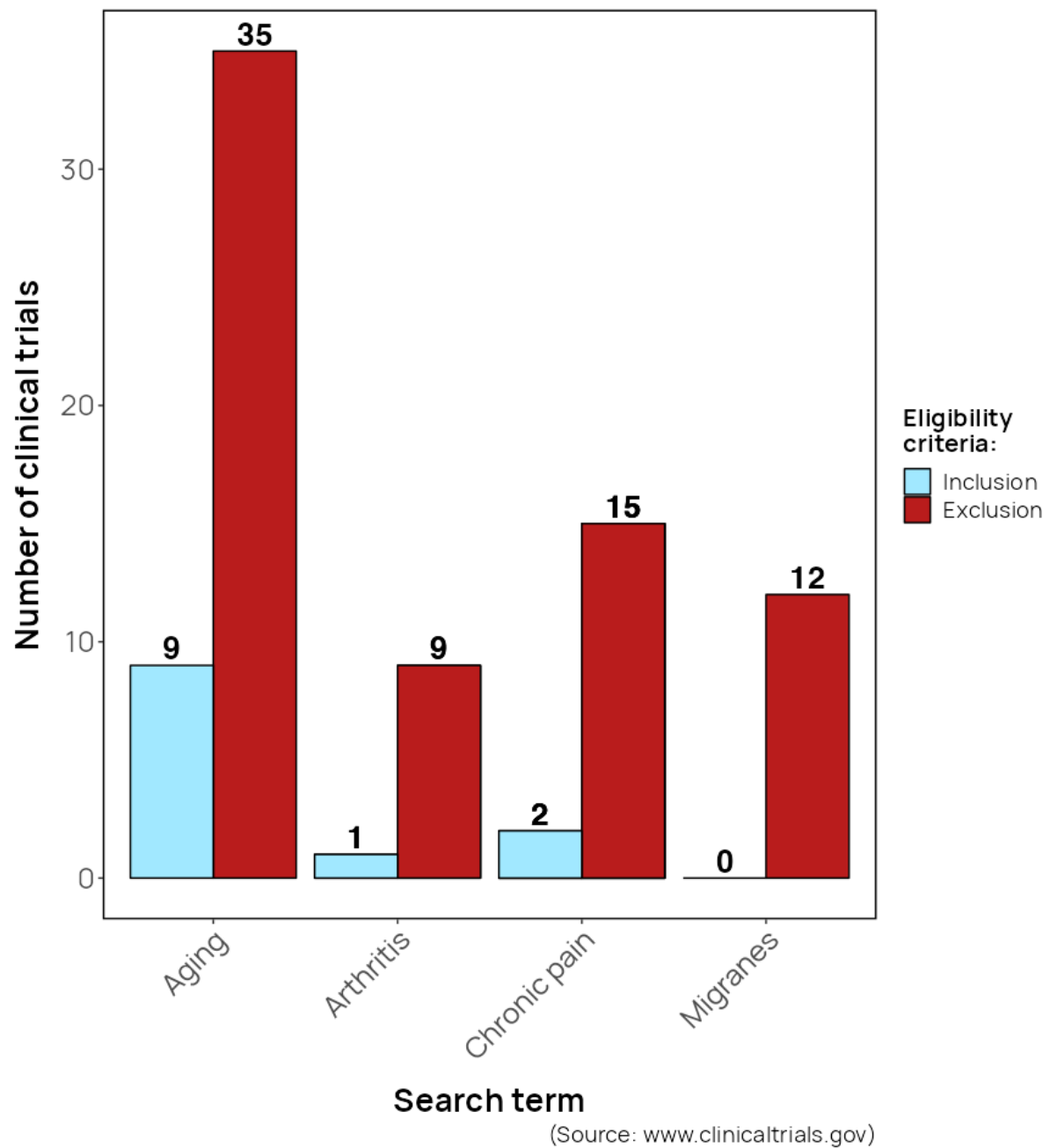


Figure 2. Comparison of inclusion and exclusion frequencies of RCPA-related search terms in bipolar disorder clinical trials.

Results and Discussion

This study identified eight RCPA terms within the eligibility criteria of BD clinical trials. These terms achieved a collective frequency of 83 which were found within the exclusion criteria more frequently (71, 85.5%) than the inclusion criteria (12, 14.5%). Of all terms, "Aging" was found with the greatest frequency (44) followed by "Migraines" (12). "Aging" and "Migraines" established 79.55% and 100% exclusion rates, respectively. All other RCPA search terms were identified a total of 27 times, yielding an 88.89% exclusion rate. Other than "Aging" and "Migraines", no RCPA search terms were found more than seven times within the eligibility section of BD clinical trials. Altogether, the difference between the inclusion and exclusion of RCPA search terms established statistical significance via a t-test paired for two sample means ($p < .05$) with a high effect via Pearson's Correlation (0.93).

Based on the results, two key elements were identified. Firstly, RCPA-related conditions are rarely considered within BD clinical trial eligibility criteria. Secondly, most RCPA-related conditions are disproportionately excluded from BD clinical trials. Ultimately, clinical trials must consider the co-treatment of RCPA conditions and BD given the regularity of coexistence, potential for disease progression, and uncertainty regarding pharmacologic intervention in BD patients.

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