

Abstract

Schizophrenia is a well-established mental health and psychological disorder that can detract from the quality of life due to multifactorial reasons. Schizophrenia symptomatology can be exacerbated in patients with concomitant hematological, dermatological, or rheumatological comorbidities. Whereas anemia, eczema/atopic dermatitis (AD), and psoriasis have all been associated with a heightened risk of schizophrenia, an interesting inverse relationship between the prevalence of rheumatoid arthritis (RA) and schizophrenia has recently been demonstrated. This study investigated the prevalence of coexisting hematological, dermatological, or rheumatological conditions in the eligibility criteria of schizophrenia clinical trials to identify any disparities in comorbid population representation. Overall, only 1.67% of schizophrenia clinical trials mentioned terms related to these comorbid conditions, and the vast majority (94.57%) were excluded. Based on the data available, a greater volume and proportion of schizophrenia clinical trials should include patients with coexisting hematological, dermatological, or rheumatological conditions to improve their quality of care, and better understand the interplay between schizophrenia and these comorbidities.

Background

Schizophrenia is a major mental health and psychological disorder that can greatly detract from an individual's quality of life. Recent research has identified interesting relationships between schizophrenia and various chronic rheumatological, dermatological, and hematological (collectively RDH) conditions, including anemia. A relatively high prevalence of anemia has been described among schizophrenia patients, especially females (Korkmaz et al., 2015). An increased risk of developing schizophrenia has been demonstrated among people whose mothers experienced anemia during pregnancy (Sorenson et al., 2011, 982). Additionally, iron deficiency, a precursor to anemia, may exacerbate symptoms of schizophrenia. Kim et al. (2018, 1707) found that iron deficiency contributed to the worsening of negative schizophrenia symptoms. Ironically, schizophrenia medicines like clozapine have been identified as potential contributors to anemia (Lozano et al., 2016, 779).

Like anemia, skin conditions such as atopic dermatitis and eczema are more likely in schizophrenic populations despite a lack of understanding regarding this relationship (Adesanya et al, 2020, e038324). Similarly, dermatitis and eczema can increase the risk of depression, exacerbating some of the negative effects of schizophrenia (Ahn et al., 2019, 1469). Interestingly, topical triamcinolone used to treat chronic eczema has been evidenced as a contributor to psychosis (Upadhyaya & James, 2019, 4).

An inverse association between the risk of developing schizophrenia and rheumatoid arthritis (RA) has been well-established in the medical literature, yet the mechanism behind this interesting association remains unclear (Chen et al., 2019, 1-9; Zamanpoor et al., 2020, e1483). Limited research has investigated the treatment of comorbid schizophrenia and RA, finding cytokine-based treatment strategies valuable in those with such coexisting conditions (Eaton et al., 2022, 114812). While the prevalence of RA may be reduced in schizophrenic populations,

quality of life can be vastly suppressed in patients with either disease (Shaban et al., 2021, 1577-1581). Those living with both conditions face a higher burden of physician visits and more frequent hospitalizations (Hitchon, et al., 2020).

Methods

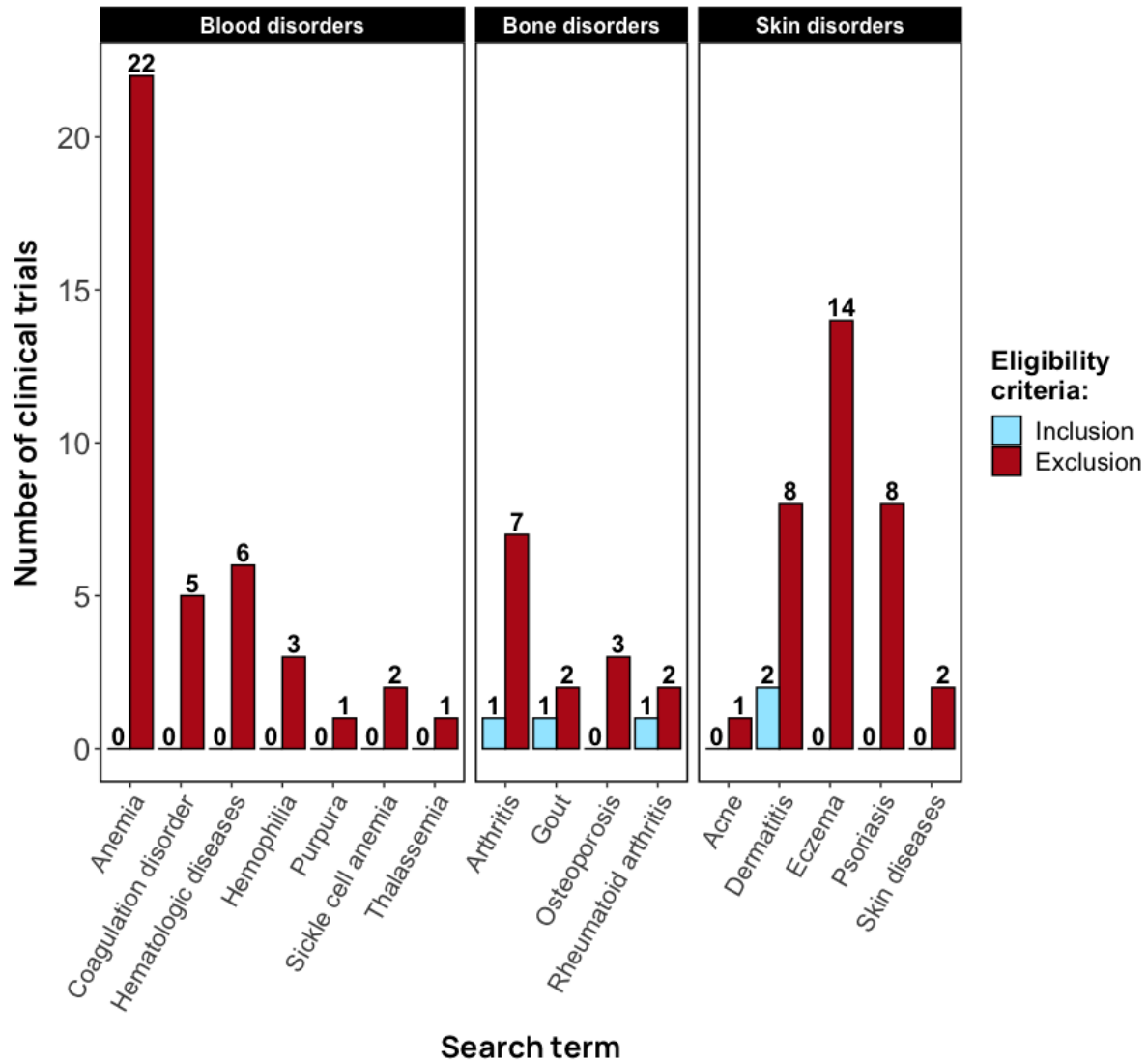
This study extrapolated data from all schizophrenia interventional clinical trials initiated between 1990 and 2022 using the United States' largest clinical trial repository, clinicaltrials.gov. Researchers used MeSHID D000012559 to investigate schizophrenia clinical trial study reports and identified those that contained terms related to rheumatology, dermatology, and hematology (collectively RDH) conditions in either their inclusion or exclusion criteria using Python 3.9.10. Clinical trials that mentioned the same term in both sections, or lacked separate inclusion and exclusion sections were flagged for manual curation. All RDH-related terms were sorted and analyzed for inclusion and exclusion frequency and further analyzed for statistical relevance. Data were organized using tidyverse (1.3.2) and analyzed using the R 'stats' package (4.2.2, 'aov' function) to establish any significant trends. Figures were created using ggplot2 (3.4.0) in R. The search terms found most frequently are identified in Table 1 and illustrated in Figure 1.

Table 1. Inclusion and exclusion frequencies of RDH-related terms found in schizophrenia clinical trials.

Search Term	Inclusion criteria	Exclusion criteria	Term groups
Anemia	0	22	Blood disorders
Coagulation disorder	0	5	
Hematologic diseases	0	6	
Hemophilia	0	3	
Purpura	0	1	
Sickle cell anemia	0	2	
Thalassemia	0	1	
Total (blood):	0 (0.0%)	40 (100.0%)	
Arthritis	1	7	Bone disorders
Gout	1	2	
Osteoporosis	0	3	
Rheumatoid arthritis	1	2	
Total (bone):	3 (17.65%)	14 (82.35%)	
Acne	0	1	Skin disorders
Dermatitis	2	8	
Eczema	0	14	
Psoriasis	0	8	
Skin diseases	0	2	
Total (skin):	2 (5.7%)	33 (94.29%)	
TOTAL:	5 (5.43%)	87 (94.57%)	

Search Terms in Schizophrenia Clinical Trial Eligibility Criteria:

(Based on clinical trials initiated between 1990 and 2022.)



(Source: www.clinicaltrials.gov)

Figure 1. Comparison of inclusion and exclusion frequencies of RA-related terms in schizophrenia clinical trials.

Results and Conclusion

This search yielded 2906 clinical trials that studied schizophrenia between 1990 and 2022. As shown in Table 1, 16 RDH terms were found in 48 schizophrenia clinical trials with a collective frequency of 92 mentions. These terms would be subdivided into groups to better understand any trends between like conditions. The groups included “Blood disorders”, “Bone disorders”, and “Skin disorders”. Collectively, 94.57% of RDH terms were excluded from schizophrenia clinical trials compared to 5.43% included. Hematologic and dermatologic disorders achieved the greatest exclusion rates of 100% (40 total) and 94.29% (35 total) respectively. Overall, the prevalence of the RDH search terms in Table 1 was significantly higher in the exclusion criteria of schizophrenia trials (one way ANOVA: $F=12.93$, $Pr(>F)=0.001$).

Currently, very few clinical trials have investigated the concurrent treatment of schizophrenia and comorbid RDH conditions. Schizophrenia is associated with a higher prevalence of anemia, atopic dermatitis, and psoriasis—conditions that can exacerbate schizophrenia symptoms and complicate medical treatment plans. Therefore it is concerning that no clinical trials were identified with terms related to anemia in their eligibility criteria, and only two studies mentioned chronic skin comorbidities. A higher inclusion of schizophrenic patients suffering from these comorbidities could help improve treatment for a vulnerable cohort in which medical care can be challenging. Conversely, there is compelling evidence that schizophrenia shares an inverse relationship with RA. However, the preponderance of this research has been epidemiologic and the mechanism remains unexplained. Actively including the patients who do develop both comorbidities in clinical trials could help elucidate the interesting association between these diseases.

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