

Abstract

Schizophrenia is a chronic brain disorder that is characterized by abnormal perceptions of reality or psychosis. The exact cause of schizophrenia is not fully understood despite numerous relationships between the disorder and other existing conditions. Schizophrenia is commonly linked to neurological conditions such as epilepsy and dementia yet the conditions are rarely permitted while coexisting in schizophrenia clinical trials. This study used clinicaltrials.gov to analyze the occurrence of neurologic terms within the inclusion and exclusion criteria of schizophrenia clinical trials, finding 33 available terms a total of 1,264 times. Of the available neurologic terms, 1,241 or 98.18% were within the exclusion criteria of schizophrenia clinical trials. Based on the relationship between neurological conditions, schizophrenia, and some data regarding their coexisting treatment efficacy, a greater proportion of neurological conditions should be established in schizophrenia clinical trials.

Background

Schizophrenia is a chronic brain disorder often characterized by a distortion of reality and psychosis. The causes of schizophrenia aren't exactly known although numerous neurological conditions are related to the disorder. Neurological conditions such as dementia and epilepsy are commonly associated with schizophrenia but tend to be excluded from schizophrenia clinical trials. Research has found an increased incidence of dementia in schizophrenia patients, finding 206,694 cases of dementia in 5,063,316 schizophrenia cases (Cai & Jingwei, 2018, 2047). Similarly, roughly 27% of schizophrenic patients aged 66 had dementia. Of those with coexisting dementia and schizophrenia, many also had other comorbidities that affected potential treatment methods (Stroup et al., 2021, 632-641).

Like dementia, epilepsy can be a notable concern for schizophrenic patients. Research has found that approximately 5.6% of epileptic patients experienced psychosis-type symptoms which could be exacerbated by certain treatments, such as clozapine (de Toffol et al., 2018, 54-60). Clozapine is one of the more common antipsychotic medicines prescribed to schizophrenic patients although between 20 and 60 percent of them remain unresponsive to the drug while others experience major adverse effects like myocarditis and seizures (De Berardis et al., 2018, 237-256).

Methods

Using MeSHID D000012559, the present study collected all available neurological terms within schizophrenia clinical trials from clinicaltrials.gov to date using Python 3.9.10. The inclusion and exclusion frequency of all terms were analyzed for all terms to establish a relationship between major conditions and the prevalence of reporting in clinical trials. 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, as well as those that mentioned the same search term in both sections, were flagged and manually inspected to

determine the correct term assignment. Data were organized using the tidyverse (1.3.2) suite of R (4.2.2) packages and analyzed using Excel to establish any significant trends. Figures were created using ggplot2 (3.4.0) in R. The neurological terms found most frequently are identified in Table 1 and illustrated in Figure 2.

Table 1. Inclusion and exclusion frequencies of neurological terms found in schizophrenia clinical trials.

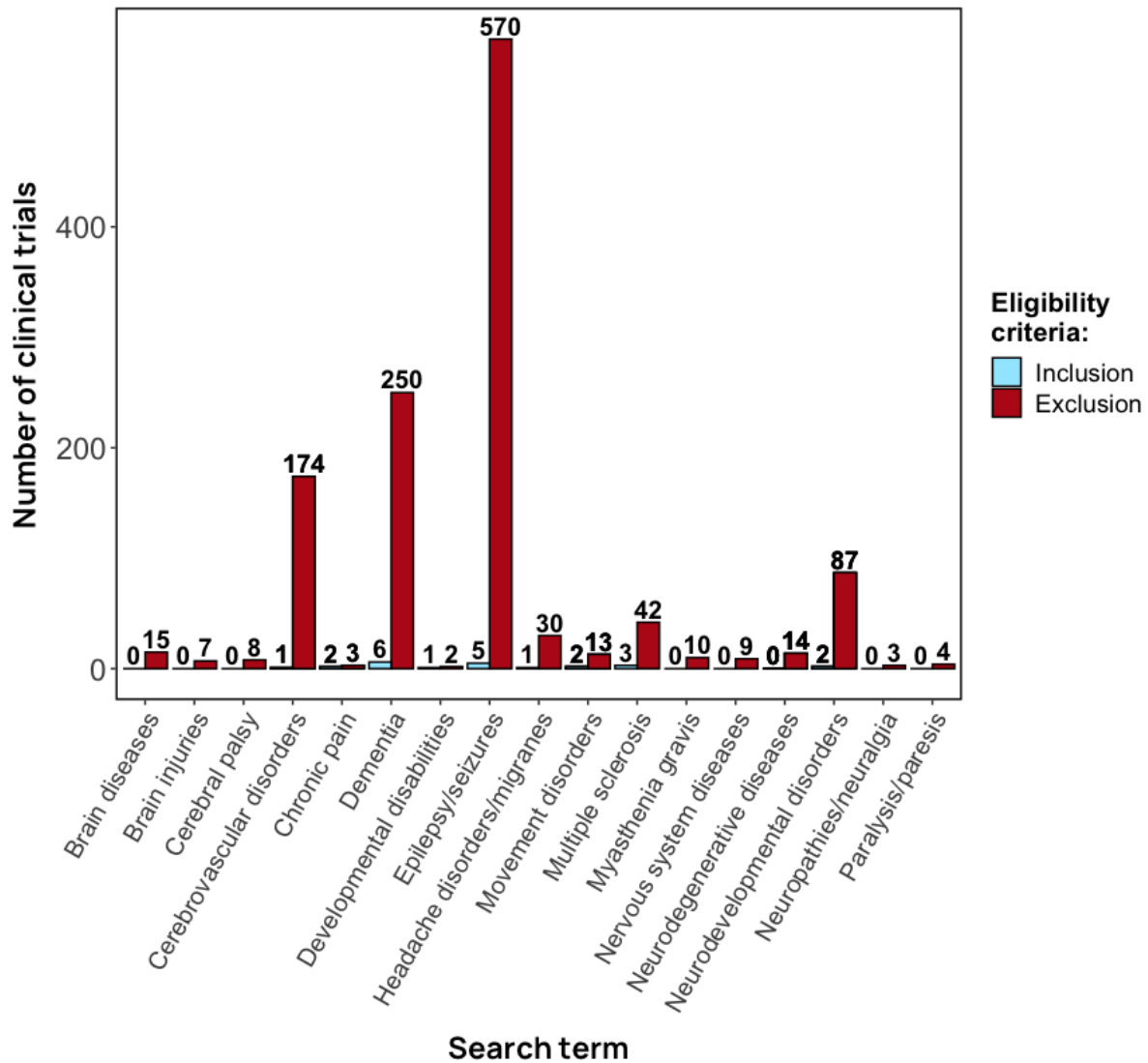
Search Term	Inclusion criteria	Exclusion criteria	Term groups
Brain diseases	0	15	Brain diseases
Brain injuries	0	7	Brain injuries
Cerebral palsy	0	8	Cerebral palsy
Cerebrovascular disorders	0	2	Cerebrovascular disorders
Hemorrhagic stroke	0	1	
Stroke	1	171	
Chronic pain	1	2	Chronic pain
Musculoskeletal pain	1	0	
Myalgia	0	1	
Dementia	6	250	Dementia
Developmental disabilities	1	2	Developmental disabilities
Epilepsy	4	310	Epilepsy/seizures
Seizures	1	260	
Headache disorders	0	1	Headache disorders/migraines
Migraines	1	29	
Dyskinesias	0	1	Movement disorders
Essential tremor	0	1	
Movement disorders	2	11	
Multiple sclerosis	3	42	Multiple sclerosis
Myasthenia gravis	0	10	Myasthenia gravis
Nervous system diseases	0	9	Nervous system diseases
ALS Amyotrophic lateral sclerosis	0	5	Neurodegenerative diseases
Alzheimer disease	0	1	
Neurodegenerative diseases	0	2	
Parkinson disease	0	6	
Down syndrome	1	0	Neurodevelopmental disorders
Intellectual disability	1	85	
Neurodevelopmental disorders	0	2	

Peripheral neuropathy	0	2	Neuropathy/neuralgia
Polyneuropathies	0	1	
Hemiplegia	0	1	Paralysis/paresis
Paralysis	0	1	
Paresis	0	2	
TOTAL:	23 (1.8%)	1241 (98.2%)	

Figure 2. The proportion of inclusion and exclusion frequencies of neurological terms in schizophrenia clinical trials.

Search Terms in Schizophrenia Clinical Trial Eligibility Criteria:

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



(Source: www.clinicaltrials.gov)

Results and Conclusion

This search identified 33 terms (Table 1) related to neurologic comorbidities in the eligibility criteria of the 2906 schizophrenia clinical trials that were initiated between 1990 and 2022. The data analysis established a clear trend in which neurological terms were excluded from schizophrenia clinical trials. The most notable disparities were observed for terms related to epilepsy/seizures, cerebrovascular disorders (“stroke”), neurodevelopmental disorders

("intellectual disability"), and dementia (Figure 1). Of the 1,264 mentions of neurological terms in the eligibility criteria, 1,241 were found in the exclusion criteria, a 98.18% exclusion rate. Neurological terms were 54 times more likely to be excluded from schizophrenia clinical trials.

While schizophrenia may affect a small percentage of the total population, the severity of its effects and the corresponding conditions are concerning. Considering the prevalence of neurological conditions like dementia and epilepsy in schizophrenic persons, additional research should seek to establish treatment methods for the conditions while coexisting. To date, clinical trials have vastly under-researched neurological conditions in schizophrenic clinical trials.

References

- Cai, Laisheng, and Jingwei Huang. "Schizophrenia and risk of dementia: a meta-analysis study." *Neuropsychiatric disease and treatment* 14 (2018): 2047.
- De Berardis, Domenico, Gabriella Rapini, Luigi Olivieri, Domenico Di Nicola, Carmine Tomasetti, Alessandro Valchera, Michele Fornaro et al. "Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine." *Therapeutic advances in drug safety* 9, no. 5 (2018): 237-256.
- de Toffol, Bertrand, Michael Trimble, Dale C. Hesdorffer, Lauren Taylor, Perminder Sachdev, Maurice Clancy, Naoto Adachi, José Augusto Bragatti, Marco Mula, and Kousuke Kanemoto. "Pharmacotherapy in patients with epilepsy and psychosis." *Epilepsy & Behavior* 88 (2018): 54-60.
- Stroup, T. Scott, Mark Olfson, Cecilia Huang, Melanie M. Wall, Terry Goldberg, Davangere P. Devanand, and Tobias Gerhard. "Age-specific prevalence and incidence of dementia diagnoses among older US adults with schizophrenia." *JAMA psychiatry* 78, no. 6 (2021): 632-641.