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Original Research Article

A review of interventional schizophrenia trials registered in clinical trials registry of India

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ABSTRACT

Background: The current therapies for schizophrenia are targeted at reducing the severity of symptoms and they do not cure the disease. The research in this field is going on for many years. The present study was designed to access the current status of interventional studies conducted in schizophrenia based on studies registered in the CTRI.
Methods: Interventional studies for schizophrenia registered on CTRI from 2007 to May 2022 were reviewed and analysed, using the keyword "schizophrenia". Parameters such as number of studies, year wise distribution of the studies registered, status of the studies at the time of analysis, types of study designs, randomization, blinding, geographical distribution, type of intervention.
Results: Out of 42952 studies registered with CTRI from 2007 to May 2022, 323 studies exclusively involved schizophrenia which accounts for only 0.75% of the total studies. 206 were interventional studies. Among the interventional studies 188 were randomized and 87 were blinded. Of all the interventional studies 141(68.4%) involved pharmacological interventions (Allopathy), 53 (25.7%) were non drug interventions, the rest were AYUSH. Of the 141 studies involving pharmacological interventions 28 were comparative studies with active control, 23 were addon studies, 14 were single arm efficacy and safety studies and 76 were BA/BE studies.
Conclusions: The study showed a rise in schizophrenia interventional study registries in the last 5 years. However, it highlighted the need to conduct more comparative studies with active control or efficacy and safety studies rather than BA/BE studies, in order to propose better alternatives to the existing therapy.

Keywords: Second generation antipsychotics, Randomized controlled trials, Schizophrenia, Interventional trials

INTRODUCTION

The term schizophrenia was introduced into the medical language at the beginning of this century by the Swiss psychiatrist Eugen Bleuler (1911). It refers to a major mental disorder, the causes of which are still largely unknown. The clinical presentation varies widely among affected individuals and even within the same individual at different phases of the illness.[1] It involves three groups of symptoms, i.e., positive, negative and cognitive.[2] Schizophrenia affects approximately 24 million people or 1 in 300 people (0.32%) worldwide. This rate is 1 in 222 people (0.45%) among adults.[1] According to an article published in The Lancet psychiatry as of 2017, 10.1 million Indians were affected with schizophrenia which is 0.7% of the India's population.[3] The treatment of schizophrenia has evolved since its inception. The first drug to be used with beneficial effect in schizophrenia was reserpine in India by Sen and Bose (1931). Reserpine is no longer used for the treatment of schizophrenia for a variety of reasons, including its propensity to cause severe and suicidal depression. Antipsychotics were formally discovered by Delay and Deniker in 1952. Since their

introduction, antipsychotics has been a part of the standard care of schizophrenia.[4,5] Second generation (Atypical) antipsychotics (SGAs) are the primary drug therapy for schizophrenia.[6] However, the benefits of SGAs are obscured by their limitations. They involve many adverse effects. These effects range from relatively minor effects (e.g., mild sedation or dry mouth) to very unpleasant effects (e.g., constipation, weight gain, extrapyramidal side effects), to life-threatening (e.g., myocarditis, agranulocytosis).[7] This may reduce the adherence to the treatment and reduce the quality of life of the patient. Various other non – pharmacological treatment modalities have been evaluated as add - on therapy for schizophrenia.[8,9] In 2005, the Indian Psychiatric Society came up with treatment guidelines for schizophrenia tailored to meet the requirements of our patients. There have been several developments in the management of schizophrenia since then. These guidelines are not particularly applicable to any specific treatment setting and may need minor modifications to suit the needs of patients in a specific setting.[10] The fact is there is no cure for schizophrenia. The current therapies are targeted at reducing the severity of symptoms. Hence the research in the field of schizophrenia therapy is ongoing. It is important to find out the status of Indian research in this area. One way of doing the same is to evaluate the Clinical Trials Registry of India (CTRI). Hence, the present study was designed to explore the type of interventional studies conducted in schizophrenia based on studies registered in the CTRI.

METHODS

The aim of the study was to review and analyse the type of research studies currently done in schizophrenia involving pharmacological and non-pharmacological interventions in India based on the data available on CTRI. The study was granted exemption from review by the Institutional Ethics Committee. The study included all the interventional schizophrenia studies registered on CTRI since its inception in July 2007 to May 2022. They were then reviewed and analysed. The clinical trial registry website of India (www.ctri.nic.in) was searched using the keywords "Schizophrenia" and "intervention" to identify all the studies registered during the mentioned period.[11] Once the studies were procured using the above keywords, the observational studies were excluded, and the remaining interventional studies were further analysed. The variables assessed were the total number of studies, year wise distribution of the studies registered, status of the studies at the time of analysis (completed/ ongoing), type of study (comparative/addon/single arm), type of intervention, randomization and methods, blinding, sample size, geographical distribution, funding of the study (pharmaceutical/government/private).

RESULTS

42952 studies have been registered with CTRI from its inception in 2007 to May 2022. However only 323 studies were conducted on schizophrenia patients which accounts for only 0.75% of the total studies. Out of 323 studies, 117 observational studies were excluded and the remaining 206 interventional studies were analysed. Of the interventional studies, 113 (54.8 %) were registered in the last 5 years (2018-2022). The year wise distribution of the registered studies is depicted in (Figure 1).

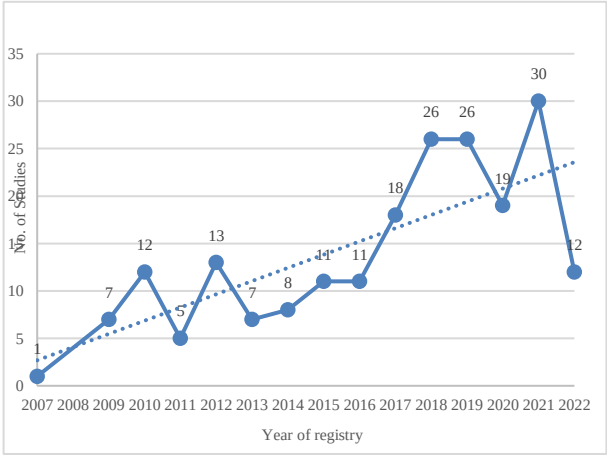

Figure 1: Year wise distribution of studies.

Total 46 studies of the total interventional studies were ongoing at the time of analysis. There were no gender specific trials registered. Only 4 studies involved adolescent schizophrenia patients (12-17 years). Out of 206 studies, 181 (87.7 %) were Indian while the remaining 25 (12.3%) were part of global studies. In India, maximum number of studies were carried in Karnataka (35 studies) followed by Maharashtra (24 studies) and Gujarat (22). The distribution across various states is given in (Figure 2).

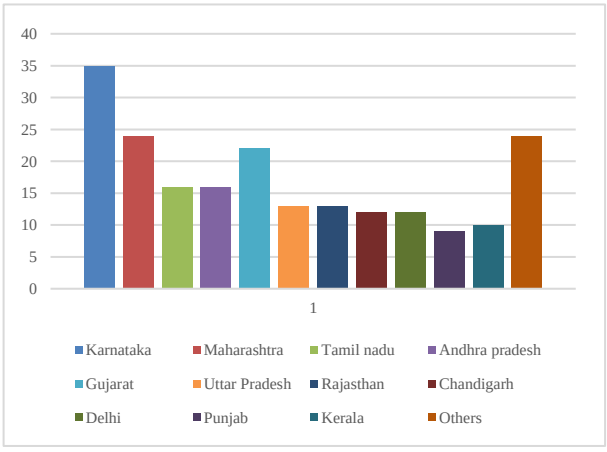

Figure 2: State wise distribution of studies.

Total 107 studies were funded by pharmaceutical companies, 44 were government funded studies, 38 were privately funded and the rest were funded by research institutes. Out of 206 studies, 71 (34.5%) were registered as post graduate thesis. 174 studies involved patients with undifferentiated schizophrenia, 13 involved paranoid

schizophrenia, 7 involved acute schizophrenia, 6 involved resistant schizophrenia and the rest involved schizoaffective disorder. 161 studies had a sample size less than 100, 36 studies had a sample size between 101-300 and 9 studies had a sample size between 301-500. Of all the interventional studies 141 (68.4%) tested pharmacological interventions (allopathy), 53 (25.7%) tested non-drug interventions and the rest were Ayurveda, Yoga, Unani, Siddha, Homeopathy interventions. 188 (91.3%) were randomized and 18 (8.7%) were non-randomized studies.

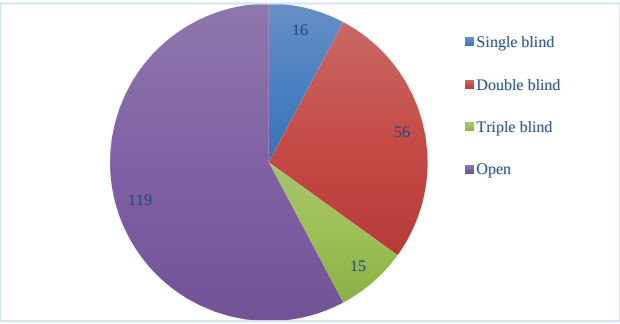

Figure 3: Blinding.

Computer generated code was the most common technique used for randomization 131. Techniques used for randomization are displayed in (Figure 4). Blinding was done in 87 interventional studies of which 16 were single blind, 56 double blind and triple blinding was done in 15 studies (Figure 3).

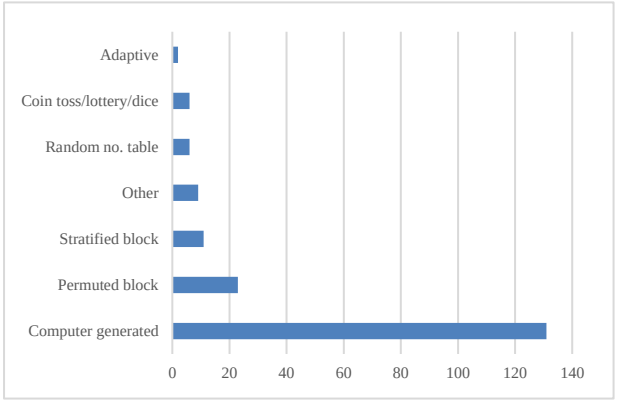

Figure 4: Type of randomisation.

Among the studies with pharmacological interventions 11% were phase 1, 21% were phase 2, 56% were phase 3 and the rest were phase 4 studies. Of the studies with pharmacological interventions, 28 were comparative studies with active control, 76 were bioavailability bioequivalence (BA/BE) studies, 23 were addon studies and 14 were single arm studies. Of the comparative studies, the most common intervention lurasidone and the most common comparator agent was risperidone. evenamide and acetazolamide were the most common drugs in the addon studies. Cariprazine was the most common drug among the single arm studies. Clozapine was the most common drug in BA/BE studies.

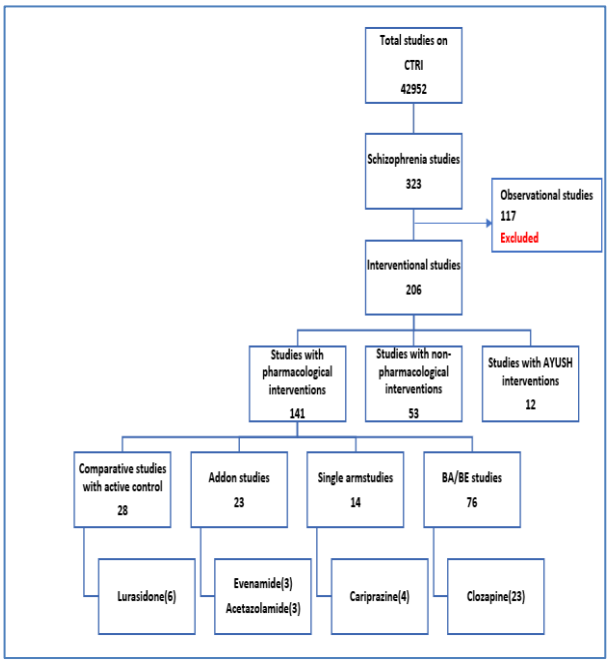

Figure 5: Overview of the current schizophrenia studies.

A flowchart showing an overview of the current schizophrenia studies is depicted in (Figure 5). Of the 53 non-drug intervention direct transcranial current stimulation (12) was the most commonly involved intervention in the registered studies, followed by Repetitive transcranial magnetic stimulation (9) and electroconvulsive therapy (9). They also included behavioural interventions such as counselling, cognitive behavioural therapy, attention training and music. Of the AYUSH studies yoga was the most common therapy used as an addon intervention to antipsychotic therapy.

DISCUSSION

Schizophrenia has been considered a unique disease for over a century, its definitions and boundaries have changed over this period and its aetiology and pathophysiology remain unknown.[12] Our study showed that <1% studies of all the studies registered in CTRI were in the field of Schizophrenia. This could be attributed to the stringent ethical guidelines associated with clinical trials involving psychiatric patients. Although, the welcoming change is the steady rise in the number of studies in schizophrenia in the past 5 years. Appropriate research methodology is an important step in any research in order to get an accurate outcome. Randomisation helps the balance the groups in a trial in terms of patient characteristics and other factors that may bias the outcomes. It is the cornerstone of a well conducted trial. Our study showed that randomisation was done in 188 studies (91.3%), which suggests that the studies were conducted among balanced groups. Randomisation can

minimize the influence of bias but it cannot eliminate it completely. Blinding of participants (Single blind) or with investigator (double blind) can further reduce the bias regarding patients knowing the identity of the treatment or due to preconceptions and subjective judgment in reporting, evaluation, data processing, and statistical analysis. Blinding was done in only 87 studies of 206 and the rest were open studies mainly consisting of BA/BE studies (76). This suggests that there could have been a high rate of bias by investigators to get a desirable outcome. Maximum funding of the studies was by pharmaceutical companies (107). Of these 107, 76 were BA/BE studies which essentially adds no value to the current therapy. As per the Indian journal psychiatry guidelines, antipsychotic drug therapy, especially second generation antipsychotics are the main intervention used in schizophrenia.[10] However, the choice of the antipsychotic agents for long term schizophrenia treatment is based primarily on the avoidance of adverse effects, prior history of patient response and existing comorbidities.[13] Our analysis revealed that a maximum number of studies (141) involved pharmacological (allopathy) interventions, 53 (25.7%) were non pharmacological interventions, the rest were AYUSH. Of the 141 studies involving pharmacological interventions 28 were comparative studies with active control, 23 were addon studies, 14 were single arm efficacy and safety studies and 76 were BA/BE studies. Our study showed that there were 9 studies which involved new drugs, of which 5 were under comparative studies, 2 as safety studies and 2 under addon studies. They are currently in the pipeline (Phase 1/2) for treatment of schizophrenia. Among the comparative studies with active control the most common interventional drug used was Lurasidone and the most common comparator drug was Risperidone. A study conducted in the psychiatry OPD of a tertiary care hospital in Andhra Pradesh and Mumbai revealed that Olanzapine and Risperidone respectively were currently most used for Schizophrenia.[14,15] However, Olanzapine is associated with dose related lowering seizure threshold and worsens diabetes by impairing glucose tolerance. It is associated with metabolic complications and high risk of stroke in elderly patients. Risperidone on the other hand is associated with tardive dyskinesia, causes more agitation in patients, carries the highest risk for hyperprolactinaemia.[13] As compared to the current prescribed drugs(risperidone/olanzapine), Lurasidone is a relatively newer second-generation antipsychotic. It has lower risk of weight gain, hypotension, metabolic side effects and tardive dyskinesia.[13] This could explain our findings as to lurasidone being the choice of intervention in comparative studies with Risperidone (a current treatment) as an active control. Our study revealed that 76 studies were BA/BE studies. However, they do not add to the existing scientific knowledge. The outcome BA/BE studies will not aid in providing better alternative drugs to the existing therapy. Evenamide and Acetazolamide were the most common drugs in the addon studies. Evenamide is a selective voltage gated sodium channel blocker currently under phase 2 trials as an addon drug, for positive symptoms of schizophrenia. Acetazolamide is a carbonic anhydrase inhibitor is under trial as an addon drug for antipsychotic associated weight gain in schizophrenia.[16] Cariprazine was the most common drug among the single arm efficacy and safety studies. It was approved by the FDA in 2015. The outcome of the Cariprazine studies may provide a drug with better safety profile for schizophrenia. A study conducted by Valiengo et al showed that transcranial direct current stimulation was effective and safe in relieving the negative symptoms in patients with schizophrenia.[8] Our study revealed that direct transcranial current stimulation (dTCS) was the most involved non- drug intervention in the registry, which shows that in this area of non-pharmacological intervention the studies are going in the right direction A study conducted by Bhatia et al. found that yoga therapy improved cognitive function in schizophrenic patients.[9] Our study showed that yoga therapy was most commonly involved as an addon therapy to the conventional drug therapy in the registered studies. Yoga has a holistic effect on the body and further studies can be conducted to make it a part of the treatment guideline in addition to the pharmacological intervention. Treatment guidelines are structured around the outcomes of interventional studies and clinical judgement based on firm scientific evidence. Hence it is important to conduct well-designed and properly executed randomized controlled trials to provide the best evidence on the efficacy and safety of the drug interventions. This will aid in refining the treatment guidelines and improve the quality of patient care.

Strengths and limitations

To our knowledge this is the first study investigating the type of interventional schizophrenia research studies in India. In addition to the type of interventions involved, our study also shows the basic methodological details such as types of randomizations, sample size and blinding used in the studies. Our study was limited to one registry and hence cannot give a comprehensive idea about all interventional researches in schizophrenia. However, it helps to outline the trend towards which schizophrenia research is moving in India. A limitation of the present study is that CTRI registration is not mandatory for all studies. The studies conducted in real time may not have been analysed.

CONCLUSION

The study revealed that schizophrenia studies were less than 1% of the total studies registered on CTRI. Although, there has been a positive uptrend in number of registries in the last five years, most of those studies were BA/BE studies conducted by pharmaceutical companies. The outcome of these studies will have no additional value to the existing therapy. The study highlights the need to conduct more comparative studies with active control or efficacy and safety studies so as to come up with newer alternatives to the existing therapy.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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