Research Paper

Antipsychotic Trials in Schizophrenia from India: A Systematic Review and Meta-analysis

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Ethnic and regional variations have been found in the pharmacological treatment response. Though many efficacy studies have been conducted in India for antipsychotic treatment modalities of schizophrenia, there is a lack meta-analytic data of the existing literature from India. This study aimed to conduct a systematic review and meta-analysis of the antipsychotic treatment trials of schizophrenia in the Indian context. All controlled trials from India evaluating the clinical efficacy of antipsychotics in patients with schizophrenia were evaluated and 28 trials were included in the metanalysis. Effect sizes were computed using Cohen's 'd' and risk of bias was evaluated. Meta analysis revealed superiority of first generation antipsychotics over placebo (mean effect size of 1.387, confidence interval of 1.127 to 1.648). Second generation antipsychotics were marginally better than first generation antipsychotics (effect size 0.106, confidence intervals 0.009 to 0.204). There was improvement in the methodology of the trials over time (Kendall tau=0.289, *P*=0.049), though no statistically significant increase in trial duration and sample size was noted. There is lack of data on long term efficacy of antipsychotic in schizophrenia from India. First generation antipsychotics have demonstrated benefits over placebo in patients with schizophrenia in the Indian context, though marginally lesser than second generation ones.

Key words: Schizophrenia, India, antipsychotics, meta-analysis

Schizophrenia is a severe mental illnesses associated with significant morbidity and poor quality of life[1-4]. It is not only associated with significant personal distress[5], but it also causes increased mortality due to suicides and associated medical illnesses[6]. Schizophrenia is also associated with increased rates of substance use disorders[7], high care giver burden[8] and occurrence of violence[9]. The social and economic costs of this disorder are considered to be substantial[10]. Adequate symptom control is considered to be paramount to reduce the morbidity and mortality associated with the disorder. Besides psychosocial interventions, use of antipsychotics is considered to be the most important treatment strategy to manage this disorder.

The last two decades has seen better understanding into the pharmacogenomics of medications including antipsychotics[11,12]. Ethnic differences in metabolism and action of drugs, which can have an impact on efficacy and thus important from standpoint of clinical decision making, are being gradually explored[12]. Hence, it becomes meaningful to ascertain how well do the interventions work in a particular ethnic background.

Over the years many studies have evaluated the efficacy/effectiveness of antipsychotics in patients from India[13]. However, it is at times not possible to reach to a conclusion about the usefulness of a particular antipsychotic medication based on a single trial. Meta-analytic studies have become the benchmark for compiling information from individual studies to make quantitative based recommendations. We were not able to identify any meta-analysis of studies originating from India evaluating the usefulness of antipsychotic medications, though

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there are 2 meta-analyses, which have evaluated the usefulness of electroconvulsive therapy (ECT)[14,15]. The results of these studies suggest that active ECT was more efficacious than sham ECT or placebo. Also, it has been found that ECT when combined with antipsychotics achieves better results than ECT alone. Addition of ECT may hasten the response to treatment in patients receiving antipsychotics[14,15].

This systematic review and meta-analysis was conducted with the objective of assessing the efficacy/effectiveness of various antipsychotic medications in schizophrenia in the Indian context. Additionally, an attempt has been made to look at the deficiency of data originating from India, and as to how to plan future studies, which can be more meaningful.

MATERIALS AND METHODS

Search strategy:
Electronic searches for published trials were carried out using PubMed, Psych Info and Google Scholar search engines. The keywords were 'schizophrenia', 'India', 'antipsychotic' (also names of individual antipsychotics), 'efficacy', 'effectiveness' and 'usefulness'. These key words were used in various combinations. The multiple searches were carried out through PubMed and other search engines in May 2013. After screening all the available data we found 296 relevant abstracts. Further studies were identified from the cross references and reference list of included studies. Searches were also made through Medknow publishers of journals from India that included Indian Journal of Psychiatry, Journal of Postgraduate Medicine, Indian Journal of Psychological Medicine, Indian Journal of Pharmacology and others. Unpublished work was not sought for as a part of this review and meta-analysis.

Study selection:
The selection criteria for inclusion of various studies into this review and meta-analysis were, controlled trials evaluating an antipsychotic treatment modality for schizophrenia, the diagnosis of schizophrenia being made in accordance to any nosological system or through clinician's interview, studies having atleast 2 treatment arms, reporting outcome measure of efficacy and published in English language peer reviewed journals. Studies evaluating the treatment modality in animal models and those evaluating the efficacy/effectiveness of antipsychotics in other conditions like bipolar depression, conduct disorder, and mental retardation were excluded. Studies with less than 5 participants in an individual treatment arm, or which had reported results in manner from which effect sizes could not be calculated were excluded from the meta-analysis. Multinational trials in which patients were recruited from India but the country specific data was not analyzed separately were also excluded.

Data extraction:
Data extraction from the identified abstracts was carried out by two investigators independently (SG and SS, fig. 1). Initial searches yielded 296 relevant articles. Cross references of these articles yielded additional 21 relevant articles. Of these articles, 93 studies were identified, which evaluated the use of antipsychotics in patients with schizophrenia. These articles were further evaluated on the inclusion and exclusion criteria for the meta-analysis. The full text of all identified studies were reviewed independently by both the investigators for the study characteristics (e.g. nature of the study, manner of randomization, blinding, duration of study, and intention to treat analysis), and clinical information (number of subjects, age range or mean, gender distribution, diagnoses made, medication groups, past treatment, efficacy/effectiveness measure, outcome and side effects) and risk of bias. Any discrepancies between the evaluators were resolved by mutual discussion. There was overall a high degree of concordance between the evaluators.

Based on the inclusion and exclusion criteria, 65 papers were excluded. The excluded studies are shown in supplemental table and the most common reason for exclusion of studies was lack of a control group in the study. The final meta-analysis included 28 studies.

For studies, which had reported more than one outcome measure, the primary efficacy measure was used for calculation of effect size. Wherever possible, the percentage of participants improved was used for calculation of effect size. Data from intention to treat analysis was used wherever possible. The number needed to treat (NNT) was also calculated for placebo controlled studies.

Risk of bias:
The studies included in the meta-analysis were assessed for risk of bias. The elements that were

studied for risk of bias included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and dropouts and selective reporting of results. Jadad scale[16] was used to quantify the risk of bias of trials included in the meta-analysis. The rating was done on the basis of reporting of randomization, blinding and reporting of withdrawals and drop-outs. The Jadad scale has been shown to have good validity and reliability[17].

Statistical analysis:

Effect sizes were calculated for each antipsychotic medication. The effect size is a measure of the efficacy of an intervention. This allows easy comparison of studies using disparate methodology and efficacy measures. Effect sizes in the present study were calculated using the standardized mean difference (d). This was selected because it gives a robust measure for both categorical and continuous measures. For dichotomous variables of efficacy, logit method was used for deriving effect size and confidence intervals. In the present meta-analysis, random effects model was used for computing the mean effect sizes. Random effects model has been shown to be superior to the fixed effects model, especially when disparate studies are combined for analysis, which was expected for this meta-analysis. The I^2 test of heterogeneity was used for assessing variation (heterogeneity) in the studies.

In studies, which had more than two interventions in defined groups, effect sizes were calculated for individual comparisons. Meta-analysis was conducted for comparisons, which had at least 3 trials. Mean effect sizes with confidence intervals were calculated for comparisons of first generation antipsychotics (FGAs) versus placebo, second generation antipsychotics (SGAs) versus FGAs.

RESULTS AND DISCUSSION

Twenty eight studies and thirty five comparisons were included in the meta-analysis, as shown in Tables 1 to 3. Of the included studies, 10 were open labeled randomized controlled trials (RCTs), 7 were double blind RCTs, 4 were controlled trials, 3 were matched controlled trials, 2 were double blind controlled trials, and two were cross-over trials. Sixteen studies compared FGAs with another FGA or a placebo, 8 studies compared SGA with a FGA or another FGA, and 4 compared medications to other forms of treatment like ECT.

Among the studies involving only the FGAs, chlorpromazine, pimozide and trifluoperazine were the most common drugs that were studied. Other FGAs included penfluridol, trifluperidol, prothipendyl, thiothexine, thioproperazine, prochlorperazine, centbutindole, and haloperidol. Among the studies, which had used SGAs, olanzapine was the most common SGA. Others included risperidone, aripiprazole and paliperidone.

The most common structured efficacy measures included positive and negative syndrome scale (PANSS), brief psychiatric rating scale (BPRS) and clinical global impression. Many studies also had used clinician reported improvements. There were no overall statistically significant differences in the effect sizes obtained when structured instruments were used, vis-à-vis clinician rated improvement (student's-t-test=1.568, P=0.129). The median duration of clinical trial was 8 w (inter-quartile range of 6 w to 13 w, range 2 w to one y). The sample sizes of the studies varied from 10 to 300, with a median of 45 (inter-quartile range of 30 to 60).

The random effect model was used for computation of effect sizes. Eight comparisons were available between FGA and placebo with a cumulative sample of 316 with a mean effect size 1.387 (confidence intervals (CI) of 1.127 to 1.648) favoring FGAs over placebo. The I^2 value for this comparison was 59.1%. The mean effect size of comparison of SGA versus FGA involving 6 studies and a sample size of 240 was 0.106 (CI 0.009 to 0.204) favoring SGAs. Fig. 2 shows the forest plot of the studies and comparisons included in meta-analysis.

The risk of bias in the included studies is shown in Table 4. The Jadad scores ranged from 0 to 4 with a median of 2 (mean of 1.75, inter-quartile range of 1 to 3). Four studies had a Jadad score of 0, 8 studies each had a score of 1 and 2, 7 studies had score of 3 and one study had a score of 4. There was a statistically significant increase in the quality of the studies with time, with recent studies being associated with lesser risk of bias (Kendall tau=0.289, P=0.049). Fig. 3 shows the Jadad scores across the publication year of the studies. There was no statistically significant relationship of the risk of

TABLE 1: STUDIES OF FIRST GENERATION ANTIPSYCHOTICS INCLUDED IN META-ANALYSIS

Authors	Intervention	Number	Methodology	Efficacy measure	Duration	Effect sizes (CI)
Bagadia *et al.*[18]	Chlorpromazine versus trifluoperazine	50 versus 50	Matched controlled trial	Clinician rated improvement	3-4 weeks	0.045 (−0.390-0.479)
Bagadia *et al.*[19]	Pimozide versus trifluoperazine	16 versus 14	Crossover trial	Clinician rated improvement	3 months	−0.179 (−1.256-0.898)
Channabasavanna and Michael[20]	Penfluridol versus placebo	15 versus 15	Controlled trial	SAPS, SANS	12 weeks	2.402 (1.010-3.794)
De Sousa and Nayani[21]	Trifluperidol versus trifluoperazine	25 versus 25	RCT	Clinician rated improvement	6 weeks	−0.192 (−0.832-0.448)
Doongaji *et al.*[22]	Injectable prothipendyl versus placebo	8 versus 5	Controlled trial	Clinician rated improvement	6 weeks	1.046 (−0.521-2.613)
Kishore *et al.*[23]	Thiothixene versus prochlorperazine	10 versus 10	RCT	PSSRS	90 days	−0.467 (−1.479-0.545)
Kishore *et al.*[23]	Thithixene versus trifluoperazine	10 versus 10	RCT	PSSRS	90 days	−0.764 (−1.858-0.330)
Kishore *et al.*[23]	Thiothixene versus thioproperazine	10 versus 10	RCT	PSSRS	90 days	0 (−0.966-0.966)
Kishore *et al.*[24]	Trifluperidol versus prochlorperazine	20 versus 20	DBCT	PSSRS	90 days	−0.744 (−1.707-0.218)
Kishore *et al.*[24]	Trifluperidol versus thiothixene	20 versus 20	DBCT	PSSRS	90 days	0 (−0.746-0.746)
Mahal and Janakiramaiah[25]	Pimozide versus placebo	25 versus 24	DBRCT	Mental status questionnaire	6 months	0.521 (−0.267-1.308)
Menon[26]	Trifluopreazine versus placebo	30 versus 30	Crossover	Behavior chart	16 weeks	0.413 (−0.227-1.053)
Menon[26]	Thiothixene versus placebo	30 versus 30	Crossover	Behavior chart	16 weeks	0.619 (−0.011-1.249)
Menon[26]	Trifluopreazine versus thiothixene	30 versus 30	Crossover	Behavior chart	16 weeks	−0.206 (−0.779-0.367)
Menon[27]	Prochlorperazine versus placebo	10 versus 10	Matched control	Social interaction	8 weeks	1.976 (0.552-3.399)
Narayan *et al.*[28]	Prochlorperazine versus chlorpromazine	10 versus 10	RCT	Clinical ratings	6 months	0.297 (−0.837-1.431)
Ramachandran and Menon[29]	Trifluperidol versus placebo	25 versus 25	DBRCT	Clinician rating	6 weeks	2.445 (1.407-3.483)
Sethi and Bhiman[30]	Trifluperazine versus trifluperazine-trihexphenidyl	15 versus 15	DBCT	BPRS	4 weeks	0.277 (−0.234-0.788)
Sharma and Dutta[31]	Pimozide versus placebo	19 versus 15	RCT	Clinical ratings	4 weeks	1.976 (0.718-3.234)
Singh *et al.*[32]	Centbutindole versus haloperidol	22 versus 22	DBRCT	PANSS, CGIS	6 weeks	0.842 (0.177-1.507)
Thomas and Narayanan[33]	Trifluoperazine versus unichlorpromazine	6 versus 4	RCT	Clinician rated improvement	12 weeks	0.382 (−1.047-1.812)

CGI: Clinical global impressions, DBCT: double blind controlled trial, DBRCT: double blind randomized controlled trial, PANSS: positive and negative syndrome scale, PSSRS: psychotic symptom severity rating scale, RCT: randomized controlled trial, SANS: scale for assessment of negative symptoms, SAPS: scale for assessment of positive symptoms, Time durations: days, weeks, months, CI: confidence interval

TABLE 2: STUDIES OF SECOND GENERATION ANTIPSYCHOTICS INCLUDED IN META-ANALYSIS

Authors	Intervention	Number	Methodology	Efficacy measure	Duration	Effect sizes (CI)
Avasthi *et al.*[34]	Olanzapine versus haloperidol	17 versus 10	Open RCT	BPRS, PANSS, CGI	12 weeks	−0.153 (−1.222-0.917)
Chandra *et al.*[35]	Risperidone versus centbutindole	22 versus 22	DBRCT	PANSS, CGI	8 weeks	−0.190 (−1.246-0.866)
Dhar *et al.*[36]	Olanzapine versus haloperidol	20 versus 20	RCT	PANSS, ESRS	6 months	0.503 (−0.126-1.325)
Jindal *et al.*[37]	Aripiprazole versus olanzapine	26 versus 27	DBRCT	BPRS, PANSS	6 weeks	0.138 (−0.401-0.677)
Shah and Joshi[38]	Paliperidone versus olanzapine	109 versus 105	DBRCT	PANSS, CGI	6 weeks	0.007 (−0.370-0.384)
Shrivastava and Gopa[39]	Risperidone versus haloperidol	50 versus 50	RCT	PANSS, CGI	1 year	−0.072 (−0.623-0.480)
Singam *et al.*[40]	Risperidone versus chlorpromazine	50 versus 50	RCT	PANSS	1 year	0.170 (−0.181-0.521)
Sagar and Chandrashekar[41]	Risperidone versus haloperidol	23 versus 23	DBRCT	PANSS, CGI	6 weeks	0.594 (0.004-1.185)

BPRS: Brief psychiatric rating scale, CGI: clinical global impression, DBRCT: double blind randomized controlled trial, ESRS: extrapyramidal symptom rating scale, PANSS: positive and negative syndrome scale, RCT: randomized controlled trial, Time durations: weeks, months, years, CI: confidence interval

bias to the sample size of the study or the duration of study period. The relationship of the year of publication with the sample size of the study and the study duration were evaluated, but failed to yield significant results (Kendall tau=0.158, P=0.250 and Kendall tau=0.051, P=0.734, respectively). This suggests that over time, studies have been getting better in methodology, but were not becoming larger or of longer duration.

The number needed to treat (NNT) for the placebo controlled studies for which this measure could be

TABLE 3: STUDIES INVOLVING ELECTROCONVULSIVE THERAPY INCLUDED IN META-ANALYSIS

Authors	Intervention	Number	Methodology	Efficacy measure	Duration	Effect sizes (CI)
Bagadia *et al.*[42]	ECT versus FGA	50 versus 200	Matched controlled trial	Clinician rated improvement	At least 3 weeks	0.731 (0.195-1.267)
Das *et al.*[43]	Medication + ECT versus medication only	23 versus 25	Comparative study	GAs	Variable	0.962 (0.457-1.467)
Janakiramaiah and Subbakrishnan[44]	ECT + chlorpromazine versus chorpromazine	22 versus 22	RCT	RP scale, CGI	6 weeks	0.091 (−0.501-0.682)
Ray[45]	ECT + chlorpromazine versus ECT	20 versus 20	Controlled trial	Clinician rating	Average 15 ECT sittings	0.606 (−0.132-1.344)
Ray[45]	ECT + chlorpromazine versus chlorpromazine	20 versus 20	Controlled trial	Clinician rating	Average 15 ECT sittings	0.606 (−0.132-1.344)
Bagadia *et al.*[42]	Insulin subcoma versus FGA	50 versus 200	Matched controlled trial	Clinician rated improvement	At least 3 weeks	−0.257 (−0.611-0.097)

CGI: Clinical global impression, ECT: electroconvulsive therapy, RCT: randomized controlled trial, RP scale: rockland Pollin scale, Time durations: weeks, CI: confidence interval, GAs: generation antipsychotics, FGA: first generation antipsychotic

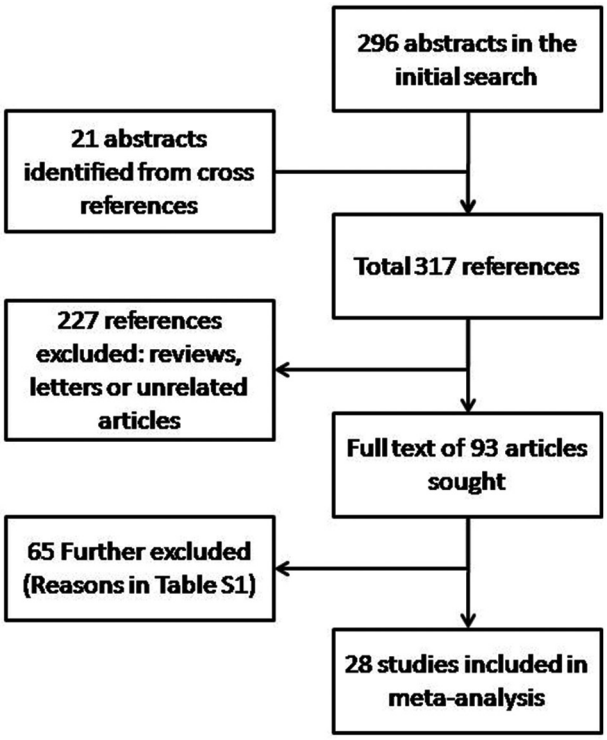

Fig. 1: Identification of studies.

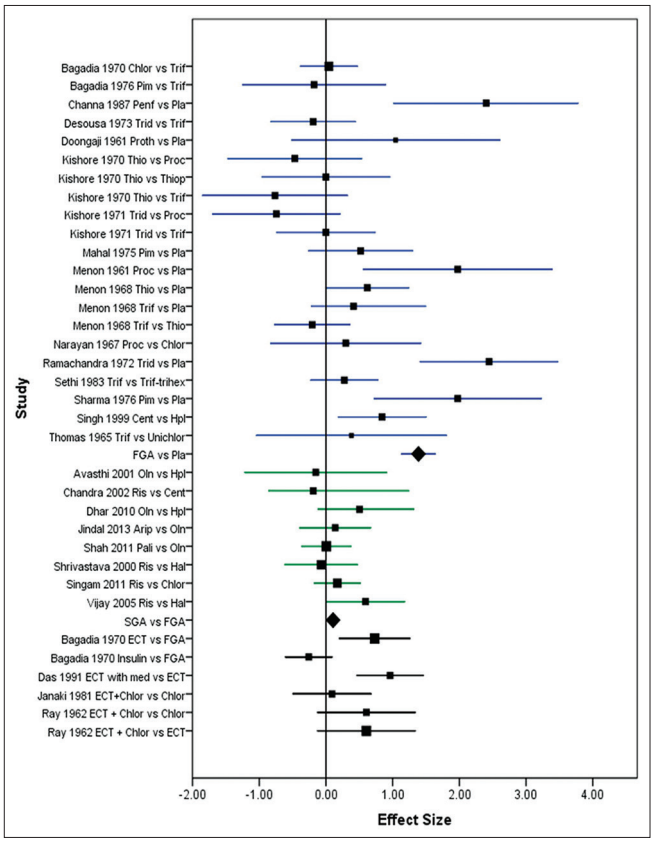

Fig. 2: Forest plot of studies included.
Studies identified by first author name, year and comparison, Arip: aripiprazole; Cent: centbutindole, Chlor: chlorpromazine, ECT: electroconvulsive therapy, FGA: first generation antipsychotic, Hpl: haloperidol, Oln: olanzapine, Pal: paliperidone, Penf: penfluridol, Pim: pimozide, Pla: placebo, Proc: prochlorpromazine, Ris: risperidone, SGA: second generation antipsychotic, Thio: thiothixene, Thiop: thioproperazine, Trid: trifluperidol, Trif: trifluoperazine, Trihex: trihexyphenidyl, Unichlor: unichlorpromazine.

computed is depicted in Table 5. NNT represents the number of patients required to treat to get one patient as a 'true' responder to treatment. This measure is useful when placebo response is expected to be high. The NNT could be computed for placebo controlled studies of FGA and varied from 1.27 to 6.67. There was no significant correlation between the size of the comparison and the NNT.

This is to the best to our knowledge the first meta-analysis evaluating the treatment modalities for schizophrenia from efficacy trials originating in India. The meta-analysis suggests that FGAs were superior to placebo and SGA are marginally superior to FGAs. The findings of the present analysis concur with that of the world literature. FGAs have proved to be efficacious in treatment of schizophrenia in well designed randomized

TABLE 4: RISK OF BIAS IN THE STUDIES INCLUDED IN THE METANALYSIS

Author (s)	Random sequence	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Jadad score
Avasthi *et al.*[34]	+	?	–	–	–	1
Bagadia *et al.*[18]	–	–	–	–	NA	0
Bagadia *et al.*[19]	+	?	+	+	–	3
Bagadia *et al.*[42]	–	–	–	–	NA	0
Chandra *et al.*[35]	+	?	+	+	–	3
Channabasavanna and Michael[20]	?	?	+	+	–	2
Das *et al.*[43]	–	–	–	–	NA	0
De Sousa and Nayani[21]	+	?	–	–	NA	1
Dhar *et al.*[36]	+	?	–	–	–	1
Doongaji *et al.*[22]	–	?	+	+	NA	2
Janakiramaiah and Subbakrishnan[44]	+	?	–	+	NA	2
Jindal *et al.*[37]	+	?	+	+	–	3
Kishore *et al.*[23]	+	?	+	+	NA	3
Kishore *et al.*[24]	–	–	+	+	NA	2
Mahal and Janakiramaiah[25]	+	?	+	+	–	3
Menon[26]	+	?	–	?	NA	1
Menon[27]	–	–	+	?	NA	1
Narayan *et al.*[28]	+	?	–	–	NA	1
Ramachandran and Menon[29]	+	?	+	+	NA	3
Ray[45]	?	?	?	?	NA	0
Sethi and Bhiman[30]	?	?	+	+	NA	2
Shah and Joshi[38]	+	?	+	+	+	4
Sharma and Dutta[31]	+	?	+	?	–	2
Shrivastava and Gopa[39]	+	?	–	–	–	1
Singam *et al.*[40]	+	?	–	+	–	2
Singh *et al.*[32]	+	?	+	?	–	2
Thomas and Narayanan[33]	+	?	–	–	NA	1
Sagar and Chandrashekar[41]	+	?	+	+	NA	3

+: attribute present, –: attribute not present, ?: unclear, NA: not applicable

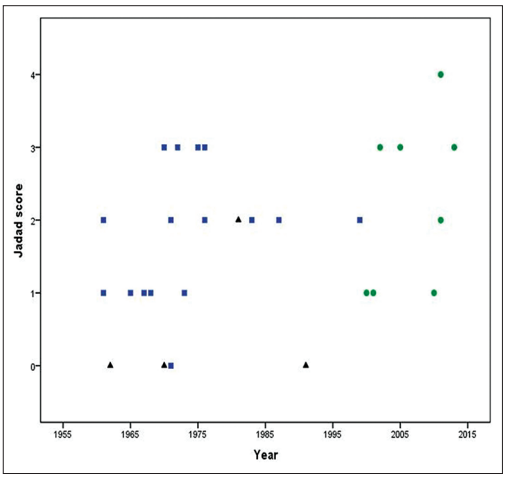

Fig. 3: Risk of bias across studies.

controlled trials and meta-analysis[46]. However, the effect sizes of the studies included in the present meta-analysis were higher (suggesting more efficacy) reflecting in lower numbers needed to treat. SGAs as a whole has been found to be marginally better than FGAs (mean effect size of 0.106). Other meta-analytic studies have also suggested SGAs to be somewhat more efficacious than FGAs[47,48]. Amisulpiride, clozapine, olanzapine and risperidone have been suggested to be more efficacious than FGAs having small to medium effect sizes[48]. Apart from greater efficacy, SGAs also seem to have better tolerability and lesser discontinuation rates[46]. A comparison of the effect sizes and the confidence intervals from this study with that for ECT in the Indian context suggests that FGAs may be more effective than ECT[14]. However, this may be influenced by the small sampled studies included in the present meta-analysis. Also, the NNT of ECT was higher than that of placebo controlled studies of FGA included in the present meta-analysis, suggesting the advantage of FGAs over ECT.

Based on the findings of the systematic review, certain conclusions can be drawn. Firstly, though there had been quite a number of studies on FGAs, the number of studies with SGAs has been fairly limited.

TABLE 5: NUMBER NEEDED TO TREAT IN CONTROLLED STUDIES

Authors	Active treatment	Number	Methodology	Duration (weeks)	Number needed to treat
Channabasavanna and Michael[20]	Penfluridol versus placebo	15 versus 15	Controlled trial	12	1.27
Doongaji *et al.*[22]	Injectable prothipendyl versus placebo	8 versus 5	Controlled trial	6	5.00
Menon[26]	Trifluopreazine versus placebo	30 versus 30	Crossover	16	6.76
Menon[26]	Thiothixene versus placebo	30 versus 30	Crossover	16	4.22
Menon[27]	Prochlorperazine versus placebo	10 versus 10	Matched control	8	1.42
Ramachandran and Menon[29]	Trifluperidol versus placebo	25 versus 25	DBRCT	6	1.67
Sharma and Dutta[31]	Pimozide versus placebo	19 versus 15	RCT	4	1.63

DBCT: Double blind controlled trial, DB: double blind, HDRS: hamilton depression rating scale, RCT: randomized controlled trial, Time durations: weeks

Prescription data from India shows that SGAs are more frequently used in the recent times[49]. However, there is a relative lack of data about SGAs from the country. Also, polypharmacy has been reported to be fairly common in India for the management of patients with schizophrenia due to clinical circumstances or psychiatrist's preferences[50,51]. However, there are no studies, which deal with concomitant use of two or more antipsychotics for patients with schizophrenia from India.

Secondly, the sample sizes of most of the studies have been low, limiting the statistical approaches that could be utilized. A closer look of the sample size further reflects that some of the older studies used relatively larger sample size, but were limited by their methodology. Some the newer studies have also been underpowered for detecting a difference. Hence, it may be a prudent option to calculate requisite sample size prior to initiation of any study and conduct interim analysis to terminate study if required statistical superiority is achieved.

Thirdly, the studies have been of limited duration (median 8 weeks), and long duration studies spanning one year or more has been rare. As schizophrenia is usually a chronic psychotic condition and most patients require long term pharmacotherapy, longer studies can help to discern the efficacy of a medication for maintenance treatment too. Not all patients respond at a similar time to a given antipsychotic[52]. The efficacy of some of the antipsychotics (e.g. clozapine) can be best judged after a period of trial of about 6 months[53].

Fourth, many of the studies, which have been conducted in India have not tried to assess the dosage requirement. Further, many of the trials do not go up to the maximum tolerable doses, reflecting that the improvement achieved can potentially be accentuated by increasing the doses of antipsychotics.

Fifthly, the Jadad scores of most of the studies have been on the lower side, suggesting the need to improve the methodologies of the trials. This can be improved by explicitly using the randomized controlled design and stating the randomization procedure in fair detail. Blinding of the patients and assessors would help in minimizing the biases that can crop up due to expectancy effects. Also, data analysis should aim at an intention to treat analysis. This would help in minimizing the unbalancing of randomization due to premature dropouts. Still, it has been encouraging to see that with passage of time, the quality of the trials has been improving.

Sixthly, studies have usually been conducted at one centre. Multi-centric studies using the same methodology in different centers can reduce the regional and centre based differences in outcomes. This would also help in achieving a larger sample size in the study. Various scientific organizations like the Indian Psychiatric Society (IPS) can play an important role in facilitating such multi-centric studies by providing expertise, identifying potential sites and collaborators, generate funding through governmental and nongovernmental sources, and disseminate the results effectively. The Drug Controller General of India (DCGI) may consider making such trials mandatory while approving a newer antipsychotic in the Indian market.

Seventhly, studies till now have not explicitly looked at the factors like treatment acceptability and adherence to medications as an outcome measure or covariate. Acceptability of treatment and adherence to medication regimen can be an important prognostic marker for sustained efficacy of antipsychotics and could be studied through controlled trial design.

Lastly, it may be prudent to focus on certain areas with regards to antipsychotics, which have received limited attention. Controlled trials focusing on depot antipsychotics, efficacy and polypharmacy and treatment resistant schizophrenia can be attempted. Recent literature has also progressed to assessment of biological markers, which can predict response to treatment[54,55]. Such studies can be conducted in the Indian genetic stock to find potential markers of response.

To sum up, there is still a need to conduct well designed multi-centric effectiveness based randomized trials with good follow up especially with respect to SGAs. Presently, there is no systematic data from India on polypharmacy. Pharmacogenomic differences may predispose Indians to tolerate lower doses of antipsychotics. This may lead to increase in cumulative doses with polypharmacy, which may influence the side effect profile too. Present pharmacogenomic literature suggests that the alleles moderating the specific side effects like tardive dyskinesia may be different in the Indian population as compared to elsewhere[56,57]. Similar studies when extend to efficacy profile may also find unique differences.

Also it must be emphasized that psychopharmacology does not act in isolation. It can be best delivered in the context of an effective service model, which incorporates attention to psychosocial aspects along with clinician's attempts to engage a patient towards recovery. Adjunct psychosocial interventions like psycho-education and family therapy may be quite helpful in engaging the patient and family into the treatment fold and expecting gradual and sustained improvement in the patient's condition[58]. Hence, wherever feasible and appropriate, the additional use of psychosocial interventions would be beneficial.

Limitations of this systematic review and meta-analysis include that only studies published in peer reviewed English language journals were included and unpublished material (including dissertations) was not sought. Sensitivity analysis was not conducted due to wide variation in the characteristics of the studies and their focuses of reporting. Some of the studies did not report the findings that could be used to calculate standardized mean differences and were not included in quantitative analysis. Also, this meta-analysis focuses on efficacy and not tolerability (side effect profile) of antipsychotic agents. The differences in the efficacy measures of reporting improvement over time may result difficulty in drawing accurate inferences from the comparisons.

The systematic review suggests that evidence base needs to be further strengthened for intervention trials of schizophrenia in Indian context, especially with regards to SGAs. Future studies should aim at effectiveness based approach especially targeting the maintenance period. Pharmacogenomic link of the treatment response can be conducted to characterize allelic markers for favorable efficacy response and particular side effects. Documentation of the research and bringing it to the public domain to consolidate the evidence base can help others to enhance their practice and clinical decision making, with the overall aim of better patient outcomes.

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