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A STUDY TO COMPARE THE EFFICACY AND SAFETY OF BREXPIPRAZOLE AND CARIPRAZINE DRUG TREATMENT FOR SCHIZOPHRENIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: A wide variety of atypical antipsychotic drugs (Thorazine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, haloperidol, prolixin, navane, loxapine, stelazine, trilafon, and mellaril and clozapine) are widely used in the management of neuropsychiatric symptoms, which are commonly seen in *Schizophrenia.* We aimed to review the efficacy and safety of atypical antipsychotic drugs (Brexpiprazole and Cariprazine) on neuropsychiatric symptoms in *Schizophrenia* patients. **Methods:** PubMed, EMBASE, and the Cochrane Database of Systematic Reviews for reports published before August 2015 were searched for eligible randomized controlled trials of atypical antipsychotic drugs therapy in patients with psychotic symptoms of *Schizophrenia*. **Results:** Overall, 4 relevant RCTs with more than 1700 participants were identified. This meta-analysis demonstrated a significant efficacy of Brexpiprazole and Cariprazine on psychiatric symptoms and PANSS score compared to placebo. In the meta-analysis, 95% confidence interval value were -16.03 to 11.81 and -9.355 to 16.00 with Std. Error 0.2394. **Conclusion:** Brexpiprazole and Cariprazine are able to improve PANSS Score at average 6 weeks in patients with neuropsychiatric symptoms of Schizophrenia. However, high adverse events may offset the efficacy of

atypical antipsychotics in Schizophrenia. We need to more phase III studies data to identify who is superior.

KEYWORDS: Thorazine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, haloperidol, prolixin, navane, loxapine, stelazine, trilafon, and mellaril and clozapine

INTRODUCTION

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. It can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies.

Schizophrenia typically begins in late adolescence or early adulthood. There are effective treatments for schizophrenia and people affected by it can lead a productive life and be integrated in society. Schizophrenia affects more than 21 million people worldwide.[1-3]

METHODS

Search strategy

The search strategy was described in detail. Briefly, we systematically searched PubMed and the Cochrane Database of Systematic Reviews for reports published before August 2015. The search criteria combined three separate domains: condition (Schizophrenia), intervention (Brexpiprazole and cariprazine) and symptoms (behavioral and psychological symptoms of Schizophrenia, neuropsychiatric symptoms, behavior). We included studies reporting overall symptoms of delusions, hallucinations, disorganized speech, disorganized behavior, and the so-called "negative". Terms were searched in titles and abstracts. We retrieved English-language articles for review, and also collected additional references from bibliographies of reviews, original research articles and other articles of interest.

Trials were selected for inclusion if they met all of the following criteria: parallel group, double-blind, placebo-controlled, randomized controlled trials (RCTs); patients had psychiatric symptoms with Schizophrenia to the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition*; and the number of patients randomized and at least one outcome measure or adverse event were obtainable.

Trials selection

Eligible Trials were randomised controlled trials (RCTs) in people with schizophrenia or

related disorders (schizoaffective, schizophreniform or delusional disorder). Trials had to compare orally administered antipsychotics (as monotherapy) with each other or versus placebo.

Trials have used Computerized testing of neuropsychological functioning, Clinical Global Impression-Severity (CGI-S), Visuospatial Working Memory (VSWM) and Digit Span of WAIS, Hopkins Verbal Learning Test - Revised (HVLT-V), Continuous Performance Task (CPT), cognitive performance, Positive Symptoms on Schedule for Positive Symptoms, Negative Symptoms on Schedule for Negative Symptoms as clinical outcomes are selected. Included studies were published between 2000 and 2015. The age of patients were mostly between 18 to 60 years. Studies included Investigational agents (Brexpiprazole, Cariprazine) and placebo.

Data retrieval

Information extracted included design characteristics, selection criteria (Schizophrenia diagnoses and presence of psychosis of Schizophrenia), medication doses, trial durations (1 to 6 weeks), age, race, gender, baseline cognitive scores, baseline neuropsychiatric symptoms and numbers randomized. Patients diagnosed with schizophrenia using Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria. Outcomes and adverse events data were from the intent-to-treat or last-observation-carried-forward samples.[4,5,6]

Statistical analysis

Meta-analyses were performed using prism statistical software. Combining the scales in an overall summary estimate, we calculated 95% CIs for changes from baseline for continuous data. For dichotomous dropouts and adverse events, we conducted an analysis of the ROC, absolute risk differences with 95% CI and *P* values to assess the safety and efficacy of the study drug. A random-effects model was applied to assess the effect sizes for each treatment–drug, placebo comparison in our study.

Because there were few dose-ranging trials and sparse outcomes for adverse events, and to avoid multiple comparisons with the same placebo group, we combined dosage groups within each trial to make one contrast with placebo according to the *Cochrane Handbook for Systematic Reviews of Interventions*. The degree of heterogeneity was assessed by visual inspection, and by a chi-square test combined with the I^2 method. The I^2 statistic

approximates the proportion of total variation in the effect size estimates that is the result of heterogeneity rather than sampling error.[7,8,9]

RESULTS

Characteristics of included trials

The results of the search process are depicted in the flowchart (Figure 1, 2). Of 10 articles identified, 4 met all review criteria. All studies were RCTs and were performed mainly in United States and India countries. Baseline characteristics were similar between intervention and placebo groups in all of the trials. The included studies were all randomized parallel trials for which the duration was 1 to 6 weeks. In the meta-analysis, 95% confidence interval value were -16.03 to 11.81 and -9.355 to 16.00 with Std. Error 0.2394.

Figure

Study name	Outcomes	Baseline	Study Period	Drug ID	Drug group	Contr	Placebo	Actual PA	Age Max	Age Min
Correll CU	PANSS	95.2	6 Weeks	Brexpiprazole	-8.72		-7.64		60	18
	CGI	4.9	6 Weeks	Brexpiprazole						
	ADE/akathisia		6 Weeks	Brexpiprazole	7.20%		2.20%			
	Weight gain		6 Weeks	Brexpiprazole	1.28 KG		0.42 KG			
BEACON	PANSS		6 Weeks	Brexpiprazole	-6.47		0.0022	674	60	18
	CGI		6 Weeks	Brexpiprazole	-0.38		0.0015			
	ADE/akathisia		6 Weeks	Brexpiprazole	4.2-6.5%		7.10%			
	Weight gain		6 Weeks	Brexpiprazole	1.23-1.89 kg		0.35 kg			
Kane	PANSS		6 Weeks	Cariprazine	-6.8		0.003	448		
	CGI		6 Weeks	Cariprazine	-0.3		-0.5		60	18
	ADE/akathisia		6 Weeks	Cariprazine	> or = 5%		> or = 10%			
	Weight gain		6 Weeks	Cariprazine						
Suresh Durgam	PANSS	97.1 ±0.8; 97.3	6 Weeks	Cariprazine	−20.7 ± 1.6	6.9 ± 1.6	−11.8 ± 1.5	732	6	18
	CGI	4.7 ±0.1; 4.8±	6 Weeks	Cariprazine	−1.0 ± 0.1	0.7 ± 0.1	−1.5 ± 0.1			
	ADE/akathisia		6 Weeks	Cariprazine	9.00%	9.00%	5.00%			
	Weight gain		6 Weeks	Cariprazine	.9 – 1.4 Kg	2 Kg	.5 Kg			

Figure 1 Total Screen (10 Studies)

Selected (4) and Excluded (6)

Meta-Analysis Results value:

Table-1

Table Analyzed	***Data 1***
Column B	BEACON
vs	vs
Column D	Suresh Durgam
Unpaired t test	
P value	0.2724
P value summary	ns
Are means signif. different? (P < 0.05)	No
One- or two-tailed P value?	One-tailed
t, df	t=0.6415 df=6
How big is the difference?	
Mean ± SEM of column B	1.124 ± 2.100 N=4
Mean ± SEM of column D	-2.200 ± 4.737 N=4
Difference between means	3.324 ± 5.182
95% confidence interval	-9.355 to 16.00
R square	0.06419
F test to compare variances	
F,DFn, Dfd	5.087, 3, 3
P value	0.2146
P value summary	ns
Are variances significantly different?	No

Table-2

Table Analyzed	***Data 1***
Column A	Correll CU
vs	vs
Column C	Kane
Wilcoxon matched-pairs signed rank test	
P value	0.5000
Exact or approximate P value?	Exact
P value summary	ns
Are medians signif. different? (P < 0.05)	No
One- or two-tailed P value?	Two-tailed
Sum of positive, negative ranks	0.0 , -3.000
Sum of signed ranks (W)	-3.000
How effective was the pairing?	
rs (Spearman)	
P Value (one tailed)	
P value summary	
Was the pairing significantly effective?	

Table-3

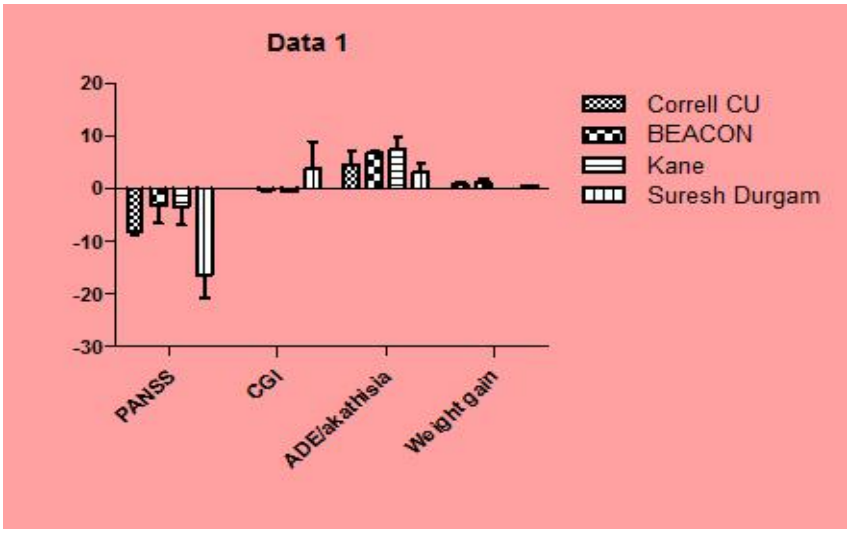
Table Analyzed	***Data 1***
Column A	Correll CU
vs	vs
Column C	Kane
Unpaired t test	
P value	0.6954
P value summary	ns
Are means signif. different? (P < 0.05)	No
One- or two-tailed P value?	Two-tailed
t, df	t=0.4210 df=4
How big is the difference?	
Mean ± SEM of column A	-0.8767 ± 3.817 N=3
Mean ± SEM of column C	1.234 ± 3.250 N=3
Difference between means	-2.111 ± 5.014
95% confidence interval	-16.03 to 11.81
R square	0.04242
F test to compare variances	
F,DFn, Dfd	1.379, 2, 2
P value	0.8407
P value summary	ns
Are variances significantly different?	No

Table-4

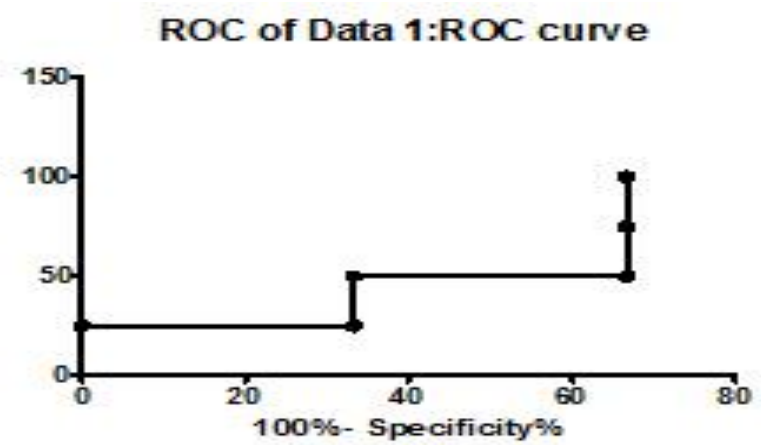
Cutoff	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
> -5.707	100.0	39.76% to 100.0%	33.33	0.8404% to 90.57%	1.50
> -1.712	75.00	19.41% to 99.37%	33.33	0.8404% to 90.57%	1.12
> 0.3304	50.00	6.759% to 93.24%	33.33	0.8404% to 90.57%	0.75
> 0.9850	50.00	6.759% to 93.24%	66.67	9.430% to 99.16%	1.50
> 2.910	25.00	0.6309% to 80.59%	66.67	9.430% to 99.16%	0.75
> 5.750	25.00	0.6309% to 80.59%	100.0	29.24% to 100.0%	

Table-5

	Results
Area under the ROC curve	
Area	0.5833
Std. Error	0.2394
95% confidence interval	0.1141 to 1.053
P value	0.7237
Data	
Controls (Correll CU)	3
Patients (BEACON)	4
Missing Controls	1
Missing Patients	0



Graph-1



Graph-2

CONCLUSION

Both drug have good PANSS score. The higher risks for adverse events may offset the efficacy of atypical antipsychotics for treatment of Schizophrenia. Hopefully, the design of a multicentre study could use currently available levels of treatment and care, in order to provide a broader generalizability of the results in the future. Future research should focus more on neuropsychiatric outcomes. It is important to continue efforts to perform high-quality trials of drug therapy, and the safety evaluation of the drugs cannot be ignored. In future we need more studies data to confirm the efficacy data.

Competing interests

The authors declare that they have no competing interests.

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