Olanzapine Vs Clozapine in Treatment of Psychosis in Children and Adolescents: A Systematic Review and Meta-Analysis

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INTRODUCTION

Onset of psychosis by age of 18 years results in a more severe form of illness (Kranzler et al., 2006) and there is a lack of sufficient evidence to guide treatment. It has been shown to cause increased severity of clinical symptoms, treatment refractory illness and more significant cognitive decline (Kranzler et al., 2006) .

Second-generation anti-psychotics remain the first line of treatment in patients with schizophrenia in children and adolescents.

Several open label studies have demonstrated efficacy of both Olanzapine and Clozapine in childhood onset schizophrenia.

A Double Blind, randomized controlled trial (RCT) by Kumra in 1996 found clozapine to be superior to Haloperidol in 21 children for treatment of positive and negative symptoms of childhood onset psychosis.

A large prospective study (Dittmann et al., 2008) in adolescents with psychosis spectrum disorder found olanzapine use resulted in marked improvement in symptoms. Consequently, there has been widespread use of Olanzapine in EOS.

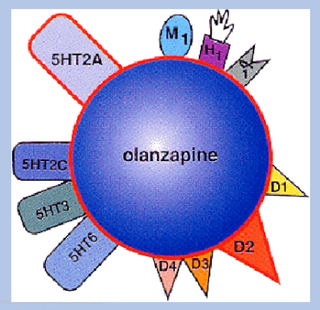
2 Double blind, RCT's have been conducted to compare Olanzapine to Clozapine in treatment of childhood onset psychosis. Shaw et al in 2006 conducted first trial comparing Clozapine with olanzapine in treatment of EOS. Results showed the association of Clozapine with greater improvement in all outcome measures. However, these results reached statistical significance only for improvement in negative symptoms, given small number of subjects.

Kumra et al 2008 conducted another Double blind RCT comparing Clozapine with "High dose" Olanzapine in treatment of refractory psychosis in children, which showed similar results, achieving statistical significance only for negative symptoms.

Open label study	Efficacy for both Olanzapine and Clozapine
Double Blind RCT (1996)	Clozapine superior to Haldol for treatment of positive and negative symptoms
Prospective Study (2008)	Olanzapine showed marked improvement in symptoms Since this study: WIDESPREAD USE OF OLANZAPINE
Double Blind RCT (2006)	Olanzapine compared to Clozapine Clozapine showed greater improvement in ALL OUTCOME measures – statistical significance for negative symptom improvement
Double Blind RCT (2008)	Clozapine compared to High Dose Olanzapine – Clozapine was statistically significant for showing improvement in negative symptoms

OBJECTIVES

- The aim of our study is to examine the roles of clozapine and olanzapine in treatment of schizophrenia in children.
- Clozapine has been increasingly used in treatment-resistant schizophrenia in adults, but the evidence in children is generally lacking. It is important to understand where clozapine lies in the treatment algorithm of adolescents.
- Previous studies have demonstrated that clozapine is advantageous compared to olanzapine but the data were statistically significant only in reducing negative symptoms.
- It has been observed that clinicians often prefer using higher doses of olanzapine to find a safer approach rather than to switch to clozapine.
- This sometimes also led to pushing for higher doses of olanzapine in which the side effects will outweigh the benefits.



MATERIALS & METHODS

- A **systematic literature review** using the Cochrane guidelines for systematic reviews was conducted using PubMed index on February 20th, 2019, by three authors independently.
- Search terms: (child OR children OR adolescent OR adolescents OR pediatric OR youth) AND (Olanzapine OR Zyprexa OR Clozapine OR Clozaril) AND(RCT OR Trial OR Naturalistic OR Open).

Inclusion Criteria:
Published articles in English only
Subjects less than 18 years old
RCT or open-labeled trials on Clozapine, Olanzapine or both
Psychotic spectrum disorders
Reports either on efficacy or on side effects

- **AIM:** to examine and compare the effect sizes of efficacy and side effects profile of Clozapine and Olanzapine in children and adolescents.
- The data was compiled and analyzed using the comprehensive meta analysis software.
- The effect sizes were then compared using the random effect analysis.

RESULTS

- We found 17 studies that met our inclusion criteria:
  - 2 on clozapine
  - 13 on olanzapine
  - 2 on both olanzapine and clozapine

	Clozapine	Olanzapine
N	51	418
Mean age (years)	13.3	14.37
Male (%)	56.16	65.02
illness duration (months)	18.21	17.35
Mean Dose (mg)	283.35	12.92
Mean study duration (months)	2.62	4.07

Table 1. Summary of Clinical Characteristics for patients in studies that met inclusion criteria

EFFICACY MEASURES:

	Clozapine	Olanzapine	P value
BPRS	-30.48*	-21.99*	>0.05
SANS	-19.85*	-8.03	>0.05
CGI	-1.94*	-1.6*	>0.05

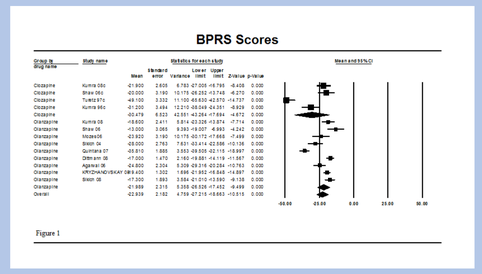


Figure 1

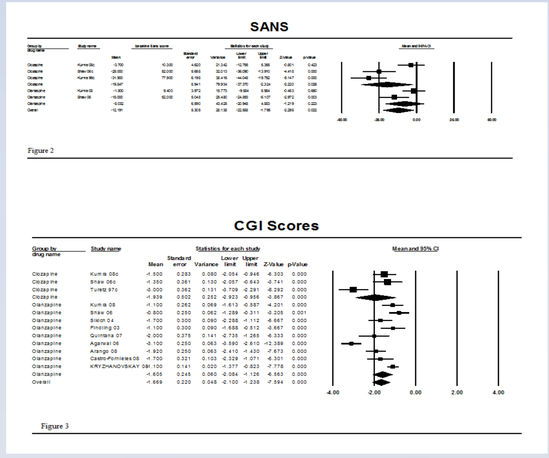


Figure 2

Figure 3

ADVERSE EFFECTS:

Measure	Clozapine	Olanzapine	P value
Weight gain (kg)	2.55	7.48 *	<0.05
BMI	0.97	2.68*	<0.05

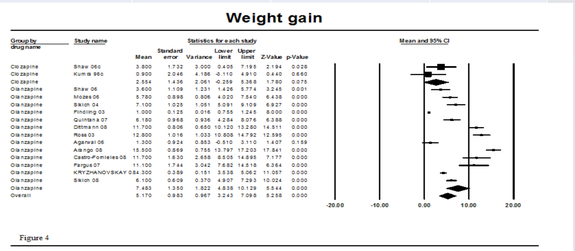


Figure 4

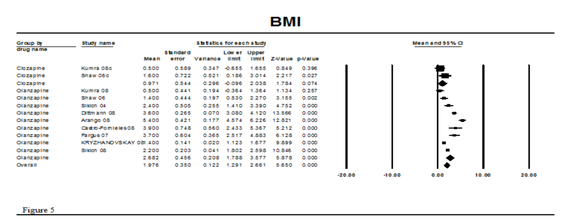


Figure 5

DISCUSSION

Efficacy measures: In the 2 subgroups, Change in BPRS scores was quantitatively greater in the clozapine subgroup (-30.48) as compared to Olanzapine subgroup (-21.99). Similarly, change in SANS score was greater in Clozapine subgroup (-19.85) than Olanzapine subgroup (-8.03). In terms of change in CGI scores, Clozapine (-1.94) was again found to be superior than Olanzapine (-1.6). Although, the inter group differences never reached clinical significance owing to smaller and fewer (N=51) studies reporting on Clozapine use in EOS. The 2 trials comparing these drugs also support our findings, (Shaw P et al., n.d.) in 2006 found inter-group differences (CGI: f=1.18, SANS: f=2.25, BPRS: 2.64) and (Sanjiv Kumra et al., 2008) found similar results (BPRS: f= .08, SANS:5.72, and CGI: f= .06), but none of these findings reached statistical significance except SANS in the study by Kumra in 2008 (p<0.05) and in the study by Shaw in 2006, achieved statistical significance only when medication free status was used as a baseline(f=4.65, p<0.05).

Adverse Events: In terms of adverse effects, statistically significant weight gain (7.48 vs 2.55, f=6.26) and BMI (2.68 vs 0.97, f=5.8) change were observed in Olanzapine sub-group as compared to Clozapine (p<0.05). Other adverse effects, including sedation and constipation were slightly higher in Clozapine sub-group, but did not achieve statistical significance. In one study two patients in clozapine subgroup and one in olanzapine subgroup had transient neutropenia which recovered within one week (Shaw et al. 2019). In another study (Sanjiv Kumra, 1996) 5 patient who received clozapine developed neutropenia (ANC<1500), 3 recovered spontaneously and 2 were dropped from the protocol.

CONCLUSIONS / LIMITATIONS

- Our analysis suggests that **Clozapine** might be quantitatively better than Olanzapine in terms of efficacy measures and adverse events.
- **Clozapine** showed **lower weight gain and lower BMI change** when compared to Olanzapine, our results were statistically significant.
- Our current analysis is limited by insufficient number of studies and inadequate sample size. This could be due to difficulty in recruiting participants in this age-group.
- More RCTs are needed to better understand the role of clozapine in treating psychotic disorders in child and adolescent population.

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Resident Contribution

The resident (Aditya Sareen, MD) is the primary author of this study. He was involved in developing the structure of the research, conducting literature review, collection of data, analysis of the data using the comprehensive meta analysis software and also in the formation of the paper and poster. The resident has also presented the study at the conference of American academy of child and adolescent psychiatry in October of 2019.