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## Pharmacological Treatment of Early Onset Schizophrenia: A Review

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**Abstract:** Early Onset Schizophrenia (EOS) is fast emerging as a significant cause of morbidity in children. Lack of systematized studies and data are a cause for concern. Multiple treatment combinations have been studied, so as to come to an acceptable conclusion, however much still remains. In this review we have tried to evaluate the existing literature, shortcomings and future directions, so as to give clarity to the phenomenon.

**Key words:** Early onset schizophrenia, pharmacological treatment, drug, side-effects

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### INTRODUCTION

A substantial proportion of patients with Schizophrenia experience the onset of their illness by the age of 18 years (Kumra and Schulz, 2008). Four percent of all schizophrenics have their onset of illness before 15 years of age (Findling *et al.*, 2007). Data from phenomenological, cognitive, neuroimaging and genetic studies suggest a similar profile of clinical and neurobiological abnormalities between early and adult onset schizophrenia patients. However, children and adolescents with schizophrenia have been found to have more severe neurodevelopmental abnormalities (Rutter and Taylor, 1984), worse long term outcome, more cytogenetic anomalies and potentially greater loading of family histories for schizophrenia than their adult counterparts (Kumra and Schulz, 2008). Various researches support the view that 'Early Onset Schizophrenia' (EOS) shows continuity with the adult form of the disorder at the level of symptoms, clinical course and underlying neurobiology (Werry and Taylor, 1994). Since the time Krapelin used the term Dementia Praecox in 1919 (Srivastava, 2009), till date the treatment guidelines have not been revised for treating EOS (Campbell and Cueva, 1995) and the treatment recommendations are extrapolated from adult literature (Campbell and Cueva, 1995), however, the pharmacokinetic and pharmacodynamic parameters of different antipsychotic medications differ in childhood and adolescent age group (Remschmidt and Schulz, 1995).

### AVAILABLE TREATMENT OPTIONS

The severe cognitive impairment and resultant poorer prognosis of EOS calls for early diagnosis, treatment and ultimately prevention before onset of psychosis. Current approach to the treatment of EOS is multipronged (McClellan and Werry, 1994), involving pharmacotherapy, family 'psycho educational' intervention, individual psychotherapy, social

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skills training, cognitive remediation, rehabilitation and assertive community treatment (McClellan and Werry, 1994), although pharmacotherapy is the mainstay of treatment (Campbell and Cueva, 1995).

Various drug trials which have been conducted on this population, have shown efficacy for the following medications:

Table 1 given above has tried to simplify a huge piece of data and an analysis of the table shows that haloperidol and clozapine are much more efficacious. Several multi center trials are also available which shows that quetiapine, ziprasidone and aripiprazole (Findling *et al.*, 2007), may also be useful in EOS, though in lesser doses. Previous studies are also available on trifluoperazine but they were conducted on autism, ADHD and mental retardation. Thioridazine is not recommended currently because of its poor adverse effect profile (Green, 2009). Haloperidol (AMA, 1994) the starting age was 13-12 years age, the usual dose was 0.5 mg day<sup>-1</sup> or 0.15 mg/kg/day, the response was as per the adult response. The other drug which has been extensively studied is risperidone, this medication has been found to be effective at 3 to 4 mg day<sup>-1</sup>, the usual response is highly efficacious. The other significant aspect highlighted in the table is the efficacy of clozapine and molindone both these drugs are useful but as 2nd line treatment choice. In nutshell the above table highlights that risperidone tops the list of drugs in efficacy and body of research followed by haloperidol followed by molindone then clozapine and olanzapine. Thiothixane, loxapine and pimozide have shown to be less efficacious.

### Ethical Issues in Treatment

It is important to understand that there are certain important ethical considerations while treating childhood schizophrenia. In very young patients only parent's consent is adequate (Clark and Lewis, 1998), valid consent is required from the older patients, patients have to be explained about the nature of illness, available treatment options and side effect profiles, outcome of treatment and prognosis of the illness. For consent to be valid patient must understand the information given to him/her and must be in a mental state, such that he/she would be capable of exercising the choice. They can also be treated against their

Table 1: Drug trials

Name of drugs	Age (years) of starting drugs	Recommended doses
Thiothixane (AMA, 1994)	>12	Starting dose: 20-30 mg day <sup>-1</sup> Maximum dose: 60 mg day <sup>-1</sup>
Loxapine (AMA, 1994)	>16	To be started at 10 mg BID, increased gradually to 60-200 mg day <sup>-1</sup> . Maximum dose: 225 mg day <sup>-1</sup>
Molindone (AMA, 1994)	>12	Starting dose: 50-75 mg day <sup>-1</sup> Maximum dose: 225 mg day <sup>-1</sup>
Pimozide (AMA, 1994)	>12	Starting dose: 0.05 mg kg <sup>-1</sup> Maximum: 0.2 mg kg <sup>-1</sup> Maximum: 10 mg day <sup>-1</sup>
Haloperidol (AMA, 1994)	>3	3-12 years age: 0.5 mg day <sup>-1</sup> to start >12 year age: 0.5-5 mg day <sup>-1</sup> to start Usual dose: 0.15 mg/kg/day
Clozapine (AMA, 1994)	>15	12.5 mg OD/BID to start, to be increased 25-50 mg every day, may be 300-450 mg in 2 weeks Maximum: 900 mg
Olanzapine (AMA, 1994, Kryzhanovskaya <i>et al.</i> (2006)	>17	Starting dose: 5-10 mg OD. Maximum: 20 mg day <sup>-1</sup>
Risperidone (AMA, 1994)	>15	1st day: 1 mg BID 2nd day: 2 mg BID 3rd day: 3 mg BID Usual dose: 6 mg day <sup>-1</sup> Maximum dose: 16 mg day <sup>-1</sup>

consent either on the basis of consent of their parents or by involving mental health legislation, or the treating team finds it urgent for treatment initiation to save the patient or others (Clark and Lewis, 1998; Clark, 2001). When consent is not at all available and treatment has to be started urgently, help of appropriate child care or mental health legislation is sought (Clark and Lewis, 1998).

#### **Available Studies**

These can be divided according to the type of antipsychotic administered.

#### **Typical Antipsychotics**

- Realmuto *et al.* (1984), compared thiothixane and thioridazine in equivalent doses and found that both were equally effective but thiothixane causes lesser sedation than thioridazine.
- Pool *et al.* (1976), compared loxapine (87.5 mg), haloperidol (9.8 mg) and placebo and found that both loxapine and haloperidol were equally effective in reducing BPRS scores and their side effect profiles were similar
- Naruse *et al.* (1982) in a double blind cross over study found that pimozide was as effective as haloperidol in improving global rating compared to placebo however in behavioral rating pimozide was more effective
- Green *et al.* (1992) found efficacy of 1-6 mg day<sup>-1</sup> haloperidol in reducing symptoms of EOS, but 25% suffered acute dystonic reaction despite low starting doses. The study result of Spencer *et al.* (1992) comparing 0.5-3.5 mg day<sup>-1</sup> haloperidol and placebo also supports the above findings
- Kumra *et al.* (1996) in a double blind head to head comparison between clozapine and haloperidol found clozapine to be more efficacious than haloperidol but greater treatment discontinuation was found with clozapine due to more adverse effects

#### **Atypical Antipsychotics**

The studies are summarized in a tabular form. The studies have been mainly done on risperidone, clozapine, olanzapine and very few on aripiprazole, although there is no marked benefit of one over the other. Risperidone has the largest data back up.

In nutshell the above, Table 2 has shown that the maximum studies (4 out of 5) have been conducted to compare the efficacy of various atypical antipsychotics and have clearly shown favourable response for risperidone. Remschmidt *et al.* (1994) and Levkovitch *et al.* (1994) have shown a good response for clozapine, while Sikich *et al.* (2004) and Haas *et al.* (2007) have gone in favour of risperidone only one study has gone in favour of aripiprazole (Findling *et al.*, 2007). Thus a clear consensus has emerged showing promising results for risperidone. Some important studies are being summarized below;

Clinical Antipsychotic Trial of Antipsychotic Effectiveness Study (CATAIE), which is a direct, randomized, double blind trial compares multiple second generation antipsychotics with mid potency first generation antipsychotics and found modest effectiveness advantage of olanzapine as compared to perphenazine, risperidone and quetiapine but no advantage of other second generation antipsychotics over perphenazines, olanzapine however, was associated with more adverse effects, particularly weight gain (Sikich *et al.*, 2004).

Treatment of Early Onset Schizophrenia Spectrum Disorder Study, (TOESS) which is a 8 week, flexible dose, randomized, double blind clinical trial comparing risperidone and olanzapine with molindone in equivalent doses in 8-18 year age group finds significant reduction in positive symptoms with all the three but adequate response in only less than

Table 2: Studies on atypical antipsychotics

Name of the study	Design	Effectiveness	Side effect
Remschmidt <i>et al.</i> (1994)	N=36 cases of resistant schizophrenia, mean age 18.1 years, Avg maximum dose 415 mg/day Clozapine, Avg duration of study 133 days	About 67% of the resistant symptoms disappeared or improved markedly in 52% cases and 29% patients showed at least slight improvement	Only 25% cases showed mild hematological abnormality which normalized during maintenance treatment
Levkovitch <i>et al.</i> (1994)	N = 13 adolescent cases of resistant Schizophrenia, avg. daily dose- 240 mg Clozapine avg. duration of study 245 days	After 2 months 76.9% showed 50% improvement in BPRS score	Tiredness 30.8%, Hyper salivation 7.7%, Fever 7.7%. No leucopenia
Shaw <i>et al.</i> (2006)	N=25, avg. duration 8 weeks, Clozapine 327 mg vs. Olanzapine 18.1 mg	Clozapine more effective than Olanzapine in reducing negative symptoms	Both caused marked weight gain during 8 week trial. Both caused dyslipidemia in 2 years follow-up
Sikich <i>et al.</i> (2004)	N=50, avg. duration 8 week, Mean age 14.7 years, compared Risperidone 4 mg day <sup>-1</sup> vs. Olanzapine 12.3 mg day <sup>-1</sup> vs. Haloperidol 5 mg day <sup>-1</sup>	All agents significantly reduced BPRS-C scores, ≥20% reduction of BPRS-C observed in 74% patients with Risperidone, 88% with Olanzapine, 54% with Haloperidol	Prevalence of EPS and weight gain much more in youth than adults
Haas <i>et al.</i> (2007)	Risperidone 1-3 mg day <sup>-1</sup> vs. Risperidone 4-6 mg day <sup>-1</sup> vs. Placebo Over 6 week period, in 160 study population	Both Risperidone group were effective in improving PANSS score equally and significantly than compared to Placebo	Higher dose Risperidone group had a greater incidence of EPS, dizziness, hypertonia
Findling <i>et al.</i> (2007)	Aripiprazole 10 mg day <sup>-1</sup> vs. Aripiprazole 30 mg day <sup>-1</sup> vs. Placebo in 302 patients	Both Aripiprazole group significantly improved PANSS (positive and negative symptoms of schizophrenia) score as compared to Placebo	Both the Aripiprazole group produced equivalent number of side effects, including mild to moderate EPS, somnolence, akathisia. Aripiprazole 30 mg day <sup>-1</sup> group showed 0.2 kg weight gain while other 10 mg day <sup>-1</sup> Aripiprazole group showed no weight gain

50 % patients, with olanzapine showing most troublesome side effects e.g., weight gain at one year follow up (McClellan, 1998; Findling *et al.*, 2007).

A clinical retrospective chart review of 172 hospitalized children with EOS treated by clozapine for 8 months showed hematological side effects in 16.1% patients which was higher than that obtained in adult studies, but agranulocytosis was found in only 0.99% cases which was similar to that found in adult studies (Gerbino-Rosen *et al.*, 2005).

### Conclusions from above Studies

There are some significant conclusions emerging from these studies:

- Side effects of antipsychotic medications in children and adolescents have not been well studied in EOS (Richardson *et al.*, 1991). The available side effect profiles of various antipsychotics in childhood and adolescent age group (e.g., dose related parkinsonian symptom and non dose related dystonias with high potency agents and sedation from low potency agents) are mainly drawn from studies of illness other than EOS (Clark and Lewis, 1998). Dyskinesia, akathisia, NMS are all recognized in EOS but there may be some difference in dosage sensitivity in comparison to adults. Overall children are at increased risk of common and uncomfortable side effects from antipsychotics (Sachdev, 1995) especially dystonias, though in future, age specific, studies are needed
- First generation and Second generation antipsychotics are equally effective in EOS, though long term studies are needed to determine long term outcome in terms of

maintaining improvement, relapse prevention, cognitive performance, treatment discontinuation and side effect profile

- First generation antipsychotics are currently preferred in EOS<sup>1</sup> mainly because of their wide range of available studies on their effectiveness and safety profile, but results of recent studies are compelling that second generation antipsychotics will become the first line drugs to be used in EOS in near future<sup>2</sup>
- Among the Second generation antipsychotics, olanzapine is notorious for weight gain

#### **Difficulties in Conducting Studies in EOS**

There are considerable hurdles when studies in EOS are conducted, because of certain specific reasons e.g., the relative rarity of the illness (Campbell and Cueva, 1995). Only 4% of the schizophrenics have their onset of illness before the age of 15 years (Knapp, 1997) and ethical difficulties in establishing trials in young people (Campbell and Cueva, 1995). Due to these reasons one cannot ignore the lacuna of previous studies, like small sample size, inadequate control group or lack of it, longitudinal follow-ups are lacking and economic feasibility is not established. Hence, it becomes difficult to formulate guidelines for an optimal treatment of EOS. The previous studies did not have a homogeneous sample (they included autism, ADHD and MR under the broader rubric of EOS), longitudinal effects on measures like cognitive status, side effects, treatment adherence, relapse prevention are lacking in most of the studies comparison of different antipsychotics in EOS and adult onset schizophrenia are lacking (Clark, 2001), many of the studies are conducted by the pharmaceutical companies and may be biased and very few conclusive studies are available.

#### **Assessment Before Starting Treatment**

Practice parameters have been developed by the American Academy of Child and Adolescent Psychiatry (McClellan *et al.*, 2001), but it is not widely accepted because of difference in cultural parameters and treatment settings in various countries, hence the available practice guidelines are extrapolated from the adult literature. A few parameters are to be rigorously assessed before treatment is initiated. Baseline assessment of weight, BMI, waist circumference at umbilicus; personal and family history of diabetes, dyslipidemia, obesity, hypertension, cardiovascular disease; BP, fasting blood sugar, lipid profile, urea, electrolytes, CBC, LFT; EEG and CT-Brain if neurological dysfunction is anticipated (Clark and Lewis, 1998; Clark, 2001). Regular monitoring of urea, electrolytes, CBC, LFT to be checked yearly after baseline assessment. For clozapine, specifically CBC to be evaluated weekly for first 18 weeks, then every 2nd week for 1 year, then monthly. After baseline assessment lipid profile and fasting blood sugar to be reevaluated at 3rd and 4-6th month respectively and then yearly. Weight to be measured frequently for 3 months and then yearly.

### **TREATMENT**

Currently there is no clear consensus about choice of antipsychotics in EOS (Clark and Lewis, 1998; Clark, 2001). Some authors suggest starting with a first generation antipsychotic (FGA), which may be substituted after 6-8 weeks with a second generation antipsychotic (SGA), only if the FGA is found to be ineffective or intolerable (Clark and Lewis, 1998). The treatment can be divided according to the phase of illness (Somsubhra, 2008).

### **In Acute Phase**

A standard oral antipsychotic should be started the dose in children is usually lesser than that in the adults (Sachdev, 1995). In young age metabolism of drugs is faster, hence they tend to metabolize antipsychotic more efficiently therefore older children and adolescents require same dose as those recommended in adults (Sachdev, 1995). Additional sedation may be considered with shorter acting benzodiazepines (lorazepam 2-4 mg orally or parentally). Parenteral neuroleptics may be considered in only those in whom benzodiazepines are ineffective (Clark, 2001). Propranolol may be considered in cases of akathisia (Green, 2009).

Antiparkinsonians may be used in the treatment and prophylaxis of dystonia and parkinsonism like symptoms. For 6-8 weeks adequate doses of medicines are given if they are well tolerated, or a trial of another antipsychotic may be considered (Clark and Lewis, 1998; Clark, 2001). The treatment differs substantially in the special age group like the elderly (Parakh and Srivastava, 2010).

### **Recuperative Phase**

This phase persists up to 4-6 weeks after the acute symptoms are controlled (Clark and Lewis, 1998). In this phase antipsychotic should be continued in same doses despite reduction in positive symptoms/disorganization/confusion. Dose reduction is considered only when high doses were administered in acute phase for rapid control of symptoms or if intolerable side effects develop (Clark and Lewis, 1998). In case of reduction of doses, close monitoring is needed to assess further relapse of symptoms (McClellan *et al.*, 2007).

### **Recovery Phase**

In this phase antipsychotics have been documented to prevent relapse (65% relapse rate as opposed to 30% relapse rate with neuroleptics in 1st year) (Kumra *et al.*, 2008). Indefinite medication is needed if the patient relapses, or if the patient shows chronic symptoms, or in newly diagnosed cases that show persistent psychotic symptoms. In these cases maintenance is required with minimum effective dose with longitudinal regular follow up.

If in any phase two antipsychotic from different classes are proved to be ineffective or intolerable the diagnosis has to be reviewed and compliance to be checked and if compliance is found to be questionable depot preparations of antipsychotic are used (haloperidol deaconate injection, risperidone depot, the long acting risperidone injection) (Shapiro and Shapiro, 1989). Lithium may be considered for affective symptoms (Clark and Lewis, 1998). Clozapine may be considered as a last resort in the doses considered safe, for at least 6-12 months (Clark and Lewis, 1998; Sachdev, 1995). If even clozapine fails to improve the symptoms all the ineffective medications are to be withdrawn, the most effective drug used previously is to be considered in lowest effective dose (Clark and Lewis, 1998). Another depot antipsychotic may be considered if poor compliance is anticipated (Clark, 2001). Cognitive behavioral interventions may also be considered to improve some symptoms (Clark, 2001).

## **CONCLUSIONS**

Though pharmacological management is the mainstay of treatment in EOS, they only refer to treating the acute symptoms and reduce the risk of relapse, neither are they always effective, nor do they guarantee good outcome all the time. These drawbacks can be adequately tackled by appropriate psychosocial and cognitive interventions. So

psychosocial interventions are recommended from the very beginning. Results of the current studies are compelling regarding the better outcome of multipronged approach than individual approaches.

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